INDUCTION CHARACTERISTICS OF PROPOFOL WITH FENTANYL AND KETAMINE

[A COMPARATIVE EVALUATION AS TOTAL INTRAVENOUS ANAESTHESIA]

THESIS

FOR

DOCTOR OF MEDICINE

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YEAR - 2002 MANJULA RANA

CERTIFICATE

This is to certify that the work entitled, "INDUCTION CHARACTERISTICS OF PROPOFOL WITH FENTANYL AND KETAMINE (A COMPARATIVE EVALUATION AS TOTAL INTRAVENOUS ANAESTHESIA)" which is being submitted as a thesis for M.D. Anaesthesiology by Dr. Manjula Rana has been carried out in the Department of Anaesthesiology, M.L.B. Medical College, Jhansi.

She has fulfilled the necessary stay in the department as required by the regulation of the Bundelkhand University, Jhansi.

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The technique embodied has been undertaken by the candidate herself and the observations have been periodically checked by me.

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"Oh my God, to him I pray
Increase my Knowledge day by day"

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Manjula Rana

Dated : 28.02.2002 **Dr. Manjula Rana**

This piece of
work
is dedicated to
my parents

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Introduction

INTRODUCTION

The world is changing at an ever increasing speed. Before the advent of anaesthesia till 1846, surgery was done only as an emergency and was a dreadful experiance for the patient during surgery, sometimes attenuation of surgical pain was accomplished with alcohol, hashih, opium derivatives or with physical methods like packing limb in ice, making limb ischemic with tourniquet, making patient unconscious by blow to the head and by strangulation.

After successful demonstration of ether anaesthesia in 1846 by W.T.G. Morton, inhalation anaesthesia become popular. But due to delayed onset and recovery, nausea, vomiting, sensation of smoothring and drowning due to face mask and inability to put mask in patients with facial injury or deformity, there was need for alternative technique to induce anaesthesia.

History of intravenous anaesthesia, begins in 15th and 16th century, when anatomist Leonardo & coworkers speculated on the functional significance of the heart and blood vessels.

The concept of intravenous anaesthesia is attractive both for the patient as well as for the anaesthetist. For patient, it had the advantage of producing rapid loss of consciousness without excitement, distress or sensation of smoothring after produced by tightly pressed facemask. For the anaesthetist there is advantage of predictable

anaesthesia, which is rapid in onset without coughing or movements.

The use of intravenous agents for total Intravenous anaesthesia (TIVA) began with introduction of rapidly acting barbiturates in 1934. One of the more important studies in the development of TIVA was that reported by Savage and colleagues in 1975 using the steroid althesin and pethidine to supplement oxygen enriched air in the spontaneously breathing patient Subsequent developments included the uses of the carboxylated imidazole, etomidate. Diazepam, medazolam, fentanyl and infusion of ketamine. Disadvantages of cumulative affects of these intravenous agents resulting in long recovery times, more chances of post operative nausea and vomiting and post operative sedation hampered their use in TIVA. Now presently propofol the most recent nonbarbiturate intravenous anaesthetic is introduced in clinical practice by Kay and Rolly in 1977.

TIVA is a natural extension of balanced anaesthesia . TIVA is a technique in which induction and maintenance of anaesthetic state is achieved with intravenous drugs alone, avoiding both volatile agents and nitrous oxide. In this process the patient either breaths spontaneously or is artificially ventilated with an air/oxygen mixture. Newer intravenous drugs now allow reliable anaesthesia to be produced entirely with intravenous anaesthesia and rapid recovery to occur even after long infusion.

TIVA has developed into an acceptable and satisfactory technique which offers many advantages like, high concentrations of oxygen can be administrated, usefulness in difficult situations, provides speedy & complete recovery, there is avoidance of deleterious effects of volatile anaesthetics, minimal cardiovascular depression, a lesser neurohumoral response to surgery, decreased incidence of post-operative nausea & vomiting, no increase in oxygen consumption, no adverse effects on hypoxic pulmonary vasoconstriction reflex the lack of trigger effects for Malignant Hypothermia, reduction in theater pollution and no adverse effects on anaesthesiologists.

There are also some difficulties and limitations of TIVA, because of the disadvantages felt with the conventionally suggested methods of administrations of the drugs used for TIVA, have been suggested to attain drug concentration in the blood quickly at the site of action in the CNS and maintain the desired effect site concentration. However, these methods need appropriate and sophisticated infusion pumps.

There is unpredictable dose response relationship due to varied patients response, use of premedication and bolus dosing. There is unpredictable recovery from anaesthesia and post anaesthetic side effects due to varied distribution and elimination kinetics of the drugs and because of gender and other non physiological factors.

Other disadvantages are cumulative properties of TIVA drugs that prolong the recovery time, drug interactions, possibility of awareness and ability to control depth of anaesthesia, requirement of a separate, dedicated i/v line.

Propofol is the hypnotic most suitable for intravenous infusion in TIVA, because it has a short elimination half life and high clearance. Propofol's rapid onset of effect and recovery time compares favourably with those of the barbiturates and Etomidate, the elimination rate of Propofol is slightly smaller than those of thiopental and Etomidate and thus the onset of effect is slower. The metabolic clearance rate for propofol exceeds hepatic blood flow, a most important difference from thiopental. In contrast to barbiturates, propofol causes less residual post operative sedation and psychomotor impairment. The incidence of post operative side effects i.e. nausea and vomiting are low.

Opioid analgesics are essential for the suppression of reflex responses to noxious anaesthetic and surgical stimuli during TIVA.

Fentanyl is synthetic opioid, its analgesic potency is 100 times greater than that of morphine but duration of action is short. In clinical doses it has little effect on cardiovascular system. There is often respiratory depression and it is often dose related. In procedures in which marked stimulation is produced, the inclusion of Fentanyl as a component of TIVA not only provides analgesia but also

permits reductions in the required doses of other agents and contributes significantly to hemodynamic stability.

As propofol has very little nociceptive effect, it is generally combined with an analgesic, the popular combination being either propofol with fentanyl or propofol with alfentanil.

Ketamine in subanaesthetic doses with propofol has gained attention in TIVA technique because of its powerful analgesic action in a small dose without causing myocardial and respiratory depression. Ketamine also causes some degree of sympathetic stimulation, which tends to counterbalance, the cardiovascular effects of propofol. One of the main drawbacks with ketamine anaesthesia has been emergence delirium, which propofol seems to be effective in eliminating. Fentanyl's non availability, it is less economic and its congeners muscular rigidity encouraged ketamine to replace fentanyl as an analgesic for TIVA. So it was thought, worth while to compare propofol in combination with ketamine and fentanyl in TIVA technique in a population of Bundelkhand region.

Aim of study

AIM OF STUDY

1. Induction characteristic of propofol.

2. Comparative evaluation of fentanyl and ketamine as analgesic with propofol in TIVA.

3. Recovery from TIVA.

Review of Literature

REVIEW OF LITERATURE

In the mid seventeenth century, soon after the description of the circulatory system by Harvey (1628). Percival Christopher Wren and Daniel Johann Major (1665) conceived the idea of injecting medicinal compounds directly into the blood and performed the first experiment, Wren injected the opium solution into the venous system of a dog by means of a quill fastened to a bladder. The injection "stupefied" the dog with in a short time without killing it.

Pierre Cyprien Ore (1872) is regarded as the true pioneer of the intravenous anaesthesia. He used chloral hydrate intravenously to produce anaesthsia. But several unfortunate post operative deaths conspired against acceptance of this method.

There followed another hiatus of 33 years. The process started again by Krawkow (1905) who injected Hedonal (methyl-propyl carbinalurethane). Four years later Burkhardt popularized the intravenous use of diethyl ether and chloroform.

Neol and Soutter (1913) reported the use of intravenous paraldehyde followed by MgSo4 (1916).

Nakagawa (1921) used Alcohol intravenously to induce surgical anaesthsia.

Barbituric acid was synthesized by Baeyer (1864) but its narcotic effects was not discovered. Later barbituric acid

(Veronal) was synthesized by Fischer and Vonmering (1903) Somnifaine was the first barbiturate to be given intravenously by Bardet (1924).

Father of intravenous anaesthesia, Helmeet Weese (1932) used Hexabarbitone. It was the first drug to make intravenous anesthesia popular.

The use of intravenous agents for total intravenous Anaesthesia (TIVA) began with introduction of rapidly acting barbiturates in 1934. Sodium Pentothal, ultra short acting hypnotic was synthesized by Earnest Henry Volwiler and Doralee Turban (1932) and introduced into clinical practice by Lundy and Waters (1934). An understanding of its pharmokinetics and its desirable pharmacological properties made thiopentone the standard anaesthetic drug to induce anaesthesia but certain adverse effects are like cardiovascular, respiratory depression, somnolence, psychic problems, motor disturbances, anaphylaxis, bronchospams, cough, hiccup, nausea and risk with intra arterial injection. One study of TIVA was that reported by Savage and collegues in 1975 using the steroid althesin and pethidine to supplement oxygen enriched air in the spontaneously breathing patient.

After, thiopentone sodium, many inducing agents were introduced with many side effects like Eugenol derivatives (Propnadid) is oil base compound cause incidence of phlebitis and release of histamine causes allergic reaction, with althesin anaphylactoid reaction, with etomidate which

is oil base compound produced local pain, diazepam also produces thrombophlebitis and with ketamine psychic emergence.

Now presently, propofol, the most recent non barbiturate intravenous anaesthetic is introduced into clinical practice by Kay and Rolly in 1977. They confirmed the potential of propofol as an anaesthetic agent. Because of its rapid onset of action, short duration with rapid and clear headed emergence and lack of cumulative effect, propofol has become very popular in total intravenous anaesthesia.

Shafer et al (1988) defined the relation between concentration and effect in ventilated patients receiving an infusion of propofol to supplement 70 percent nitrous oxide and given incremental doses of pethidine. The average blood propofol concentration associated with an obtunding of the autonomic responses during abdominal surgery was 4.05 μg/ml and 2.97 μg/ml during body surface surgery.

Bailie R et al (1989) studied two techniques of total intravenous anaesthsia for laproscopy in 80patients Group I received alfentanil, propofol and vecuronium, and Group II alfentanil, midazolam, ketamine and vecuronium. Haemodynamic stability after induction and the pressor response to tracheal intubation were significantly different. There was no significant difference in recovery times between the two groups and little difference in other postoperative sequelae.

Janstrup M et al (1990) compared the combination of propofol with alfentanil and fentanyl for total intravenous anaesthesia dosage was propofol, bolus 1.5 mg/kg, infusion 9 mg/kg , fentanyl bolus 7.5 μg / kg. infusion 15 μg/kg/hr reduced successively to 1.8 μg/kg/hr. Alfentanil, bolus 60mg/kg, infusion 240 mg/kg / hr reduced successively to 100 μg/min. Induction was smooth and maintenance easy to manage in both groups. Plasma concentrations were stable with a ratio of alfentanil to fentanyl of 100:1. Recovery times were equal and short.

Mayer M et al (1990) studied whether the combination of propofol and ketamine (group A) can give better hemodynamic stability during the induction and maintenance of general anaesthesia when compared with the propofol and fentanyl.(group B) After the beginning of the operation the group B showed major hemodynamic changes; in particular, bradycardia with less then 40 bpm was observed in more patients then in group A. Postoperatively, fewer patient in group B required rescue doses of analgesics than these in group A.

Fruergaard K et al (1991) compared the combination of propofol and fentanyl with etomidate and fentanyl for total intravenous anaesthesia. Patient received either propofol (Bolus 1.5mg/kg, infusion 9 mg/kg//hr for 10 minute thereafter 6mg/kg/hr) or etomidate (bolus 0.10 mg/kg, infusion 3mg/kg/hr reduced to 0.6 mg/kg/hr). Fentanyl 10μg/kg was given for induction followed by an infusion of

30μg/kg/hr for 10 min reduced to 6 μg/kg/hr for the first hour and successively reduced over time. Induction was smooth and maintenance easy to manage in both groups. There was no difference in time from end of infusion until extubation , but until the patients could report their date of birth was significantly shorter in the propofol group.

Schuttler J et al (1991) studied total intravenous Anaesthesia with ketamine and propofol with optimizing dosing strategies. The major known side effects of propofol (reduced hemodynamics during induction) and ketamine (psychic disturbances and cardiovascular stimulation) were absent and respiratory function was adequate after the end of surgery.

Sanders L D et al(1992) assessed recovery over 48 hours after anaesthesia with propofol or thipentone as sole anaesthetic agent in 36 unpremedicated gynaecological patients. Immediate recovery, as measured by the Steward scale to be quicker for the patients given propofol.

Nightingale J et al (1992) conducted a double blind study to compare post operative recovery after either total intravenous anaesthesia (TIVA propofol & alfentanil) or an inhalational technique (propofol & isoflurone) in 50 patients undergoing day case gynaecological surgery.Recovery occurred significantly earlier in the TIVA group as assessed by critical Flicker Fusion Threshold and Simple reaction time ($P<0.01$); there were no significant differences ($P>0.05$)

between the two groups in choise reaction time, subjective duration of recovery or side effects.

Jenstrup M et al (1992) studied alfentanil infusion in total intravenous anaesthesia. A study comprising 14 women admitted for elective hysterectomy was done. Alfentanil was given in combination with propofol in total intravenous anaesthesia technique. The predicted median alfentanil concentrations [289 (256-363) ng/ml] was significantly lower than the measured median plasma concentration of (368 (168-666) ng/ml). In conclusion, population based pharmacokinetics were found not to be accurate as they underestimate plasma concentrations of alfentanil.

Browne BL et al (1992) estimated the dose of propofol (initial dose followed by a stepped infusion) when given with two different infusion rates of alfentanil for total intravenous anaesthesia in 59 children aged 3-12 years . Patients in series 1 received an alfentanil loading dose of 85 μgm/kg and an infusion of 65 μg/kg/hr. Patients in series 2 received an alfentanil loading dose of 65 μg/kg and an infusion of 50 μg/kg/hr. In series 1, the ED_{50} was 60 mg/kg/hr (5.5 – 6.2 mg/kg/hr) and ED_{95} 8.6 (6.8 –7.8) mg/kg/hr. Corresponding values for series 2 were ED_{50} 7.5 (8.0 – 0.8) mg/kg/hr and ED_{95} 10.5 (9.6 – 13.1) mg / kg/hr.)

Vuyk et al (1993) examined the dynamics of alfentanil when used to supplement either an infusion of propofol (measured concentration 4μg/ml) or nitrous oxide in oxygen

in patients undergoing lower abdominal surgery. The EC_{50} of alfentanil needed for intubation was 92 ng.ml in the total intravenous group compared with 429 mg/ml in the nitrous oxide group. Thus alfentanil requirements appear to be less when used to supplement propofol (4 μg/ml) compared with nitrous oxide (6.7 percent).

Sandin R and Nordistrom O. (1993) studied awareness during total intravenous anaesthesia. Five cases of awareness have been identified during TIVA with mechanically controlled ventilation and neuromuscular block. Two of the cases resulted from inability to deliver the target dose of anaesthetics, while the patients need for anaesthetic was greater than anticipated in three patients.

Palomba R et al (1994) compare balanced anaesthesia with Total intravenous anaesthesia in videolaparochole cystectomy .The first group was administered total intravenous anaesthesia : propofol+ fentanyl+ pancuronium bromide, the second one received balanced narcosis: thiopentone sodium+ isoflurane + pancuronium bromide . The data obtained from analysis of the intraoperative parameters showed no significant differences between the two groups ,on the contrary a statistically significant difference was found with regard to the quality of recovery (P>0.5 at 5' from the extubation). Thus together with the reduced requirements of analgesic drugs in the postoperative period and the lack of air pollution , seems to

suggest that TIVA is to be preferred for laparoscopic surgery.

Dyer R.A.et al (1995) studied one hundred ASAI Orthopaedic surgical patients anaesthetized using continuous propofol and intermittent fentanyl (TIVA) with controlled ventilation via a tracheal tube in groups I and II and laryngeal mask airway in group III and IV . Neuromuscular blockers were used in groups I & III only. There were no significant differences between groups in total anaesthetic requirements, as assessed by cardiovascular variables and movement, groups I and II had significantly higher heart rates and mean arterial pressures than groups III and IV for varying periods up to 5 min, after insertion of the airway management device . There was no correlation between mean arterial pressure and plasma concentrations of catecholamines related to insertion of either the tracheal tube or laryngeal mask airway . The laryngeal mask airway was found to be highly effective device for controlled ventilation in TIVA and easier to manage than the tracheal tube in the absence of neuromuscular blockers.

Hiu T.W. et al (1995) studied the additive interactions between propofol and ketamine when used for anaesthesia induction and for total intravenous anaesthesia in female patients . The addition of ketamine did not significantly alter the ED_{50} for apnea of propofol . There was significant difference in the arterial pressures among the three groups

(P<0.001) Using the combination the cardiostimulant effects of ketamine balanced the cardiodepressant effects of propofol .

Speicher A. et al (1995) studied postoperative pulmonary function after lung surgery in total intravenous anaesthesia with propofol in comparison to balanced anaesthesia with isoflurave. The postoperative impairment of lung function after lung resection under propofol anaesthesia is statistically significantly smaller than under isoflurance anaesthesia .

Levy D.M. et. Al (1995) studied the effects of ketamine compared with alfentanil on onset of neuromuscular block during total intravenous anaesthesia . Supplementation of propofol anaesthesia with alfentanil or ketamine does not appear to influence the onset time of vecuronium.

Jakobsson J et al (1995) studied supplementation of propofol or thiopentone anaesthesia with 0.5 or 1.0 mg alfentanil or 0.05 or 0.1 mg fentanyl for minor gynaecological out patient procedures. Propofol compared to thiopentone was associated with a shorter time to discharge and anxiety during recovery was more frequent in the thiopentone group. The need for postoperatives reseave analgesics was less in the alfentanil group. Supplementation with 1.0 mg alfentanil to propofol was

found to be the best combination tested for short outpatient procedures.

Adams H A. et al (1995) compared two regimens of total intravenous anaesthesia , with propofol and S(+) ketamine (S-ketamine) and with propofol and alfentanil with reference to endocrine stress response , circulatory effects and recovery TIVA with propofol and S-ketamine had sympathomimetie properties with positive circulatory effects and led to moderate endocrine stimulation On the other hand total intravenous anaesthesia with propofol and alfentanil showed sympatholytic properties , with negative circulatory effects and a remarkable reduction of endocrine stress response.

Moussa A.M. et al (1995) compared recovery characteristics of propofol total intravenous anaesthesia and isoflurane inhalation anaesthesia for dental day surgery . TIVA using propofol had faster and better quality of recovery.

Phillips A.S. et al (1996) compare post operative nausea and vomiting, oxygen saturations for the first three post operative nights, time of return of gastrointestinal function , mobilsation and discharge from the hospital following induction and maintenance of anaesthesia with propofol and alfentanil or with thiopentone ,nitrous oxide, isoflurane and alfentanil. Recovery from anaesthesia was faster in propofol group, times to eye opening and giving correct date of birth of 14.0(sp- 13.5) and 25.5(SD-29.5) minutes, and 18.5(SD-14.8) and 35.5(SD37.2) minutes in

propofol and isoflurane groups respectively. There was significantly less nausea in the propofol group(15.4%) than in the isoflurane groups (33.7%) .The incidence of hypoxaemia was close to 70% in both groups for the first three postoperative nights indicating the need for oxygen therapy after major abdominal surgery.

Escarment J et al (1996) studied the combination of propofol , ketamine and vecuronium for TIVA on 29 patients treated for elective surgery. Operative conditions were satisfactory for the surgeons. Recovery was fast and emergence reactions very limited . No hypoxaemia was observed during the immediate postoperative period

Back A et al (1996) used titrated total intravenous anaesthesia in 78 patients undergoing surgical procedures lasting 4-25 min. Boluses of thiopentone (Group1)propofol(Group2), propofol +alfentanil (Groups3) and ketamine + midazolam(Group4)were used. Induction of anaesthesia, resulted in a mean blood pressure decreased about 15% . Apnoea of more than 20sec was observed in group 3,but no naloxone was required; Recovery was rapid enabling patients to maintain their own airway ..

Crozier T.A. et al (1996) compare the effect of more active stereoisomer S(+)Ketamin in combination with propofol on the circulatory , endocrine and metabolic responses to abdominal surgery with those of alfentanil propofol. TIVA with ketamine –propofol had little effect on the perioperative courses of the endocrine parameters which

behaved as they do under anaesthesia with isoflurane-nitrous oxide.

Kietzmann D et al (1996) compared the effects of sufentanil –propofol with fentanyl- propofol anaesthesia in patients undergoing major abdominal surgery with both regimens , the sympathoadrenal stress response to major abdominal surgery was nearly completely suppressed, resulting in stable haemodynamics during the operation. Sufentanil and fentanyl were equally well suited as analgesic components of TIVA with propofol.

Nordstrom O et al(1996) studied the incidence of awareness in total intravenous anaesthesia based on propofol , alfentanil and neuromuscular blockade . One thousand patients were anaesthetized with total intravenous anaesthesia. Two cases of awareness were detected (0.2%).One of these was identified immediately after extubation. The second patient had no memory of intraoperative events or dreams at the first interview, recalled a bad dream on the day after ,and had explicit recall of intraoperative events at the interview 8 days later. In both cases, haemodynamic signs of inadequate anaesthesia were present . This study indicates that if appropriate dosing of propofol and alfentanil are adhered to and proper action is taken in case of haemodynamic alterations suggestive of inadequate anaesthesia, the

incidence of conscious awareness in total intravenous anaesthesia with neuromuscular blockade is low.

Kreien Meyer J (1997) studied total intravenous anaesthesia with propofol and sufentanil for resection of pheohromocytoma . The patient showed a smooth haemodynamic course at the end of operation, the patient was haemodynamically stable and the postoperative course was uneventful.

Hirota K. et al (1997) evaluated the changes in epidural pressure as a good index for cerebrospinal fluid pressure during total intravenous anaesthesia with propofol+ fentanyl +ketamine (Group1) compared to isoflurane + nitrous oxide anaesthesia (Group2) . Twelve patients for gastrectomy were allocated to two groups. In group 1 epidural pressure did not increase during the anaesthesia and was significantly lower than in group 2. The present data suggest that propofol, fentanyl, ketamine may safely be used for patients with intracranial hypertension.

Sakai T. et al (1998) studied pharmacokinetics of propofol and ketamine during propofol - fentanyl ketamine anaesthesia for pediatric surgery . Plasma levels of propofol were maintained at 2.5 μg/ml during surgery, fifteen minutes after cessation of propofol infusion plasma level decreased to 1.5 μg/ml. Plasma levels of ketamine were maintained at 150-200ng/ml during the surgery , after the cessation of ketamine infusion, plasma levels of ketamine

decreased as quickly as propofol and at 15 minutes and 120 minutes after the cessation of the infusion were 93 ng/ml,24ng/ml respectively. On the other hand , plasma norketamine levels increased gradually during surgery and stayed at –100-150 ng/ml after the end of ketamine infusion to play an important role in postoperative sedation and pain relief. In conclusion, pharmacokinetics of propofol and ketamine in pediatric patients was similar to that in adult patients.

Trinder T.J. et al (1998) investigated three combination of propofol and alfentanil as total intravenous anaesthesia for major thoracic surgery .There were no significant differences in heart rate or blood pressure between groups either induction or maintenance. Recovery characteristics were similar between group , although there was a trend towards earlier orientation in the group which received the highest infusion rate of alfentanil . The higher of the two alfentanil infusion rates may result in a better combination of propofol and alfentanil with respect to recovery times than the lower.

Schraag S et al (1998) studied 30 female patients undergoing elective surgery , to assess the reliability of eletroencephalogram spectral edge frequency and median frequency to predict loss of consciousness and movement in response to skin incision during TIVA. They concluded that spectral edge frequency was a poor predictor and median frequency was no predictor of response in the individual

patient during Total intravenous propofol / sufentanil anaesthesia.

Rowbotham D.J. et al (1998) compared remifentanil in combination with isoflurane or propofol for short stay surgical procedures . Patients were randomized to receive a remifentanil loading dose of 1.0μgm/kg followed by a continous infusion of 0.5μg/kg/ min in combination with isoflurane (Group I) or propofol (group P) . The ramifentanil infusion rate was reduced by 50 percent , 5 minutes after tracheal intubation. Times to spontaneous respiration, adequate respiration and tracheal extubation were significantly shorter in group I compared with group P.

Kilickan L . et al (1999) compared effect on intraocular pressure and haemodynamics of endotracheal Intubation (ET) or laryngeal mask insertion (LMA) during TIVA without the use of muscle relaxant . In 20 Patients scheduled for elective orthopedic surgery ,anaesthesia was induced with i.v. alfentanil and propofol, Laryngeal Mask insertion or Endotracheal intubation was achieved . Mean arterial pressure and heart rate after insertion of the airway management devices was significantly higher than induction values in the group E.T. While during 2.3 minute no significant change were observed in group LMA. In all patients following propofol and alfentanil induction intraocular pressure following extubation was significantly

higher than preinduction values in the group ET, but not in the group LMA.

Juckenhofel S . et al (1999) studied the differences between TIVA with propofol remifentanil(group1) and Balanced Anaesthesia with sevoflurane / fentanyl (group2) in gynaecological laparoscopic surgery. Recovery time in group 1 was significant shorter than in group 2. There were no significant differences between the groups in shivering, pain score, analgesic demand and postoperative nausea and vomiting. So advantages with total intravenous anaesthesia over balanced anaesthesia are haemodynamic stability, significantly shorter times of emergence .

Hernandenz C.et al (1999) compared the characteristics of induction, maintenance and awakening for three techniques of TIVA. Propofol – ketamine, midazalam – ketamine and propofol - fentanyl. Haemodynamic variables were most stable in group 2. Perfusion of midazolam-ketamine was accompanied by significantly higher number of hypertensive peaks. Time to awakening was significantly shorter in group I them in group 2. No patient experienced hallucinations and all reported satisfaction with the anaesthetic technique used. Total intravenous technique with ketamine and propofol is comparable to the most commonly used combination of propofol and fentanyl and may be appropriate choice when haemodynamic stability is of great importance.

Onaka M.et al (1999) compared postoperative pain in two groups. All anaesthetic agents were administered intravenously in group I (propofol 2-10mg/kg/hr, ketamine 240 μgm/kg/hr and fentanyl 0.4 μgm/kg/hr) .In a control group anaesthesia was maintained by N_2O-Oxygen-isolfurane . To evaluate pain VAS and prince Henry score on rest ,cough and movement were taken 2hrs and 5 hours postoperatively .The group I showed lower scores than the control group. It is of a great advantage to use continous TIVA for postoperative pain management and low dose ketamine may induce Pre-emptive analgesic.

Hamdani G.A. et al (1999) compared propofol in combination with fentanyl or ketamine for short out patient anaesthesia . A double blind study was design to evaluate ketamine as an analgesic in sub anaesthetic doses in comparison to fentanyl . The efficacy and clinical tolerance of the two anaesthetic techniques was studied in 50 patients undergoing minor gynaecological procedures. The results show no statistically significant difference between the two group regarding efficacy and tolerance. Therefor ketamine in subanaesthetic doses can be recommended as an alternative analgesic for short procedure.

Hunt- Smith J et al (1999) studied safety and efficacy of target controlled infusion versus manually controlled infusion of propofol for anaesthesia . Induction times were significantly longer and induction doses were significantly

lower in the target controlled infusion group. Recovery times and total doses were not significantly different. There was statistically but not clinically significant differences in mean arterial blood pressure and heart rate. Conclusion was that target controlled infusion and manual controlled infusion are similar in terms of safety and efficacy .

Sim K.M. et al (2000) studied TIVA using 3-in-1 mixture of propofol , alfentanil and mivacurium. Induction and maintenance of anaesthesia were smooth, intubation conditions satisfactory and intraoperative haemodynamic changes acceptable. Recovery from anaesthesia and neuromuscular blockade was rapid . There were no major intra or immediate postoperative complications.

Piotroueski D. et al (2000) assesd usefulness of methohexitone and propofol in TIVA applied during planned knee joint arthroscopy in day case surgery. Both methohexitone and propofol cause cardiac and respiratory depression .Patients on propofol regain psychomotoric efficiency earlier then patients who received methohexitone.

Romic P.et al (2001) investigated effects of TIVA with propofol and remifentanil with midazolam co-induction in Laproscopic surgery of the gallbladder .It makes possible haemodynamic stability of patients after induction in anaesthesia, good oxygenation during surgery, fast, early

and complete recovery and avoiding of side effects of anaesthesia and postoperative nausea and vomiting.

Russel I.F. et al (2001) studied that there is absence of memory for intra operative information during surgery with TIVA. There was no evidence of implicit or explicit memory.

Saha K et al (2001) evaluated efficacy and tolerability of combination of propofol, ketamine as compared to propofol. fentanyl combination. The two ambulatory anaesthetic techniques were studied in 60 patients undergoing minor gynaecological surgery. The result showed that the combination of propofol ketamine offered the advantages both in efficacy and tolerability as compared to propofol fentanyl.

TOTAL INTRAVENOUS ANAESTHESIA

Total Intravenous Anaesthesia is by defination a technique involving the induction and maintenance of the anaesthetic state with intravenous drugs alone avoiding both volatile agents and nitrous oxide. Independent regulation of each component of anaesthesia namely , unconsciousness, amnesia , analgesia, control of the sympathetic nervous system and muscle relaxation is achieved by selective specific intravenous agents .

The development of hypnotic and analgesic drugs with short and predictable duration of action and better insights into their clinical pharmacology have improved future prospects for TIVA, Advances in pharmacokinetics

knowledge have further improved the delivery system by targeting appropriate effect site concentration in relation to the nature and intensity of the surgical stimulation.

ADVANTAGES AND LIMITATIONS

Total intravenous Anaesthesia offers significant advantages because of the high concentrations of oxygen that can be administered and the minimal cardiovascular depression induced by the intravenous drugs. These anaesthetic techniques are increasingly popular for laparoscopy, cardiac operation and neurosurgery as well as in situation where anaesthesia with volatile agents is difficult.

More ever total intravenous is appropriate for surgical procedure in which the use of nitrous oxide may be contraindicated(leg, ear surgery, treatment of air embolism, emphysematous bullae, and pneumothorax and bowel surgery of long duration)or when the deleterious organ effects of volatile anaesthetics must be avoided.

Other claimed advantages of TIVA include a decreased incidence of postoperative nausea and vomiting ,a lesser neurohumoral response to surgery, the lack of trigger effect for malignant hyperthermia and a reduction in atmospheric pollution.

To achieve an adequate state of anaesthesia the method of administration of the drugs is important. Intermittent injections of the drugs result in high peak plasma concentrations with possible side effects and unstable

plasma levels with peaks and troughs influencing the kinetics of the drugs at the receptor sites .More ever significant accumulation of drug may result if the dosing intervals are short .With shorter acting drugs given as an intravenous infusion, tighter control of the clinical effects can be maintained with a higher degree of precision, reliability and predictability . Fixed rate infusion are not useful in the context of TIVA because stable anaesthetic conditions are not rapidly achieved , indeed steady state plasma concentration of drugs are reached only after four to five elimination half lives . There for in clinical anaesthesia , more complex administration regimens are needed to attain the drug concentration in the blood quickly at the site of action in the central nervous system and for maintenance of the desired effect site concentration.

The next difficulty relates to the defination of the therapeutic window for drug effect . Patients display a moderate variation in dosing needed for a defined response relationship, the interpretation of dose effect relationship in many studies is further confounded by the use of premedication and redistribution because of rapid initial distribution and redistribution of the drug in the body. Because drug effects are generally more closely related to concentrations than to dose , the best approach to define a therapeutic window is to use the concept of target plasma or effect site drug concentrations. A dosages scheme designed to maintain the anaesthetic concentration at the low end of the therapeutic window in the absence of stimulation and to

raise the concentration to the upper end rapidly and only for as long necessary should result in a more stable anaesthetic state , a reduction of the total amount of drug administrated , and a faster recovery from its effects.

Other problems may arise with TIVA. The disappearance of a pharmacologic effect depends on the redistribution of the drug and its metabolic clearance. Thus recovery from anaesthesia and postanaesthetic side effects are not easily predicted . Finally many drugs show cumulative properties that also prolong recovery with Total Intravenous Techniques, difficulties of administration, drug interactions , adequate defination of the clinical end points of anaesthesia and potential delays in awakening from anaesthesia.

ANAESTHESIA AND AWARENESS

Intraoperative awareness is a major concern with intravenous anaesthetic techniques. A satisfactory degree of anaesthesia requires adequate cardiovascular and respiratory stability, no or minimal patient movement and no awareness or recall of event during the procedure . the most sensitive clinical signs of depth of anaesthesia appear to be changes in muscle tone and pattern of respiration. In patients given muscle relaxants these signs are lost and one must rely primarily on signs of autonomic hyperactivity. Blood pressure changes are a less sensitive endpoint for judging depth of anaesthesia when intravenous agents are used and signs mediated by the autonomic nervous system

are unreliable indicators of anaesthetic adequacy when potent opioids or adrenergie blocking agents are used.

The noxious stimulation produced by surgery induces a variety of reflex responses . Pain is the conscious perception of such a noxious stimulus . If patients are given appropriate doses of opioids for antinociception and of hypnotics for maintaining unconsciousness, awareness and recall will be unlikely . Awareness is the quality of being vigilant or conscious and does not necessarily result in memory or recall. Patients may respond to commands under anaesthesia without recall postoperatively , but they may also show evidence of implicit memory without being aware and without showing explicit recall.

An inadequate depth of anaesthesia is likely to occur when blood or biophase concentration are widely fluctuating. As with all physiologic functions, awareness is a threshold phenomenon and thus its appearance is expected to be related to insufficient concentrations of the intravenous drugs at the brain site. When appropriate concentrations for unconsciousness of these agents are maintained awareness in unlikely.

For propofol , blood concentration of 3.5 to 5.4 μg/ml should be maintained even in the presence of analgesic concentration of fentanyl. When signs of light anaesthesia are present administration of intravenous hypnotics allows rapid deepening of the state of anaesthesia ,so to prevent awareness one must remain vigilant for signs of light anaesthesia.

PROPOFOL :

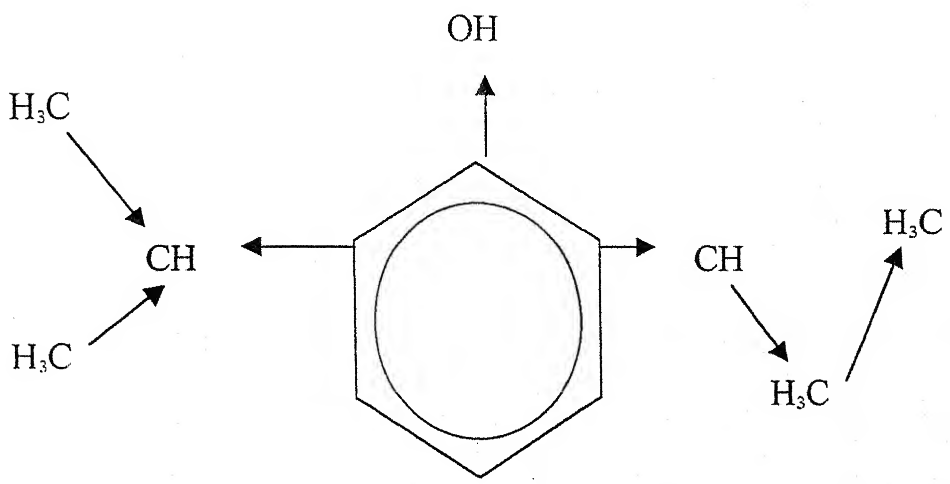
Propofol (Diprivan) is the most recent intravenous anaesthetic to be introduced into clinical practice by kay and Rolly in 1977.

PHYSIOCHEMICAL CHARACTERISTICS :-

Propofol is 2,6-di-iso-propyl – phenol. It is one of a group of alkyl-phenols that have hypnotic properties The alkyl-phenols are oils at room temperature and are insoluble in aqueous solution, but they are highly lipid soluble . The present formulation is in a 1percent (wt/vol)emulsion of 10 percent soyabean oil , 1.2 percent purified egg phosphatide and 2.25 percent glycerol. This is similar to the fat emulsion intralipid which is used for parentral nutrition. Propofol has a ph of 7 and appears as a slightly viscous , milky white substance . Propofol is available as 1 percent solution in 10 ml. and 20 ml. vials, 20 ml. clear glass ampules , 50 and 100 ml vials and in 50 ml prefilled syringes. It is stable at room temperature and is not light sensitive. If a dilute solution of propofol is required, , it is compatible with 5 percent dextrose in water.

METABOLISM :

Propofol is rapidly metabolised in the liver by conjugation to glucronide and sulfate to produce water soluble compounds, which are excreted by the kidneys. Less than 1 percent propofol is excreted unchanged in urine, and



Propofol (2,6, di-iso Propyl-Phenol

only 2 percent is excreted in faeces. The metabolites of propofol are thought not be active . Because clearance of propofol exceeds hepatic blood flow , extra hepatic metabolism or extra renal elimination has been suggested . Propofol itself results in a concentration dependent inhibition of cytochrome P-450 and thus may alter the metabolism of drugs dependent on this enzyme system.

PHARMACOKINETICS :

Propofol is 98 percent bound and being highly lipophilic , is distributed rapidly throughout the blood and vessel rich tissues . Blood levels than decline with the initial distribution half life of 2 to 8 minutes and elemination half life has varied from 1 to 3 hour. Other worker have identified three compartment model of initial and slow distribution half lives of 1 to 8 minutes and 30 to 70 minutes and an elimination half life of 4 to 23.5 hours . The clearance of propofol is extremely high – 1.5 to 2.2 l/min. which accounts for the rapid wakening from anaesthesia .

The pharmacokinetics of propofol may be altered by a variety of factors (e.g. Gender, weight, pre- existing disease, age and concomitant medication) . Propofol may alter its own clearance by decreasing hepatic blood flow . Fentanyl reduces the clearance to approximately 1.3 L/min by reducing propofol distribution and increasing blood level. Propofol kinetics are unaltered by renal disease.

PHARMACODYNAMICS :-

EFFECT ON THE CENTRAL NERVOUS SYSTEM

Propofol is primarily a hypnotic .It acts by promoting the function of the B_1 subunit of GABA through activation of the chloride channel and thereby enhancing inhibitory synaptic transmission .It also inhibit the NMDA subtype of glutamide receptor through modulation of channel gating Propofol is not an antianalgesic .

The onset of hypnosis following doses of 2.5 mg / kg is rapid (one arm brain circulation) with a peak effect seen at 90 to 100 seconds. ED_{50} of Propofol is 1 to 1.5 mg/kg following a bolus. The duration of hypnosis is dose dependent , being 5 to 10 minutes following 2 to 2.5 mg/ kg.

In subhypnotic doses propofol provides sedation and amnesia . Propofol tends to produce a general state of well being . Recovery after propofol 2.5 mg/kg is significally faster . Propofol has a direct anticonvulsant effect which is dose dependent. Tolerance has been developed to propofol following either repeat anaesthesia or propofol inufsion (days)..

Propofol decreases intracranial pressure (ICP) in patients with normal or increased intracranial pressure . Normal cerebral reactivity to CO_2 . and autoregulation are maintained during a propofol infusion. Propofol reduces cerebral metabolic rate of oxygen consumption ($CMRO_2$) by

36 percent . It also provide cerebral protective effects following an acute ischemic insult.

EFFECT ON RESPIRATORY SYSTEM

Propofol is a potent respiratory depressant similar to barbiturates . Apnea occurs after an induction dose of propofol , the incidence and duration of apnea appear to be dependent on dose , speed of injection and concomitant premedication .The onset of apnea is usually preceded by marked tidal volume reduction and tachypnoea. Following induction dose it decreases respiratory rate significantly for 2 minutes and minute volume is significantly reduced for upto 4 minutes.

The ventillatory response to CO_2 is also decreased during a maintenance infusion of propofol . Propofol (1.5 – 2.5 mg/kg) results in an acute rise (13-22%) in $PaCO_2$ and decrease in PH . Propofol (50-120 mg/kg/min) also depress the ventilatory response to hypoxia. Propofol induces bronchodilation in patients with chronic obstructive pulmonary disease.

EFFECT ON THE CARDIOVASCULAR SYSTEM

The most prominent effect of propofol is a decrease in arterial blood pressure during induction of anaesthesia . Independently of the presence of cardiovascular disease an induction dose of 2-2.5 mg/kg produces a 25-40 percent reduction of systolic blood pressure . Similar changes are seen in mean and diastolic blood pressure . The decrease in arterial pressure is

associated with a decrease in cardiac output /cardiac index(15%) , stroke volume index (20%) and systemic vascular resistance (15-25%).Left ventricular stroke work index is also decreased (30%) .The decrease in systemic pressure following an induction dose of propofol appears to be due to both vasodialation and myocardial depression. Both the myocardial depressant effect and the vasodialation appear to be dose dependent and plasma concentration dependent. The vasodialatory effect of propofol appears to be due both to a reduction in sympathetic activity and to a direct effect on intracellular smooth muscle calcium mobilization.

Heart rate does not change significantly after an induction dose of propofol . As propofol either results or inhibits the baroreflex thus reducing the tachycardia in response to hypotension. Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction.

Heart rate may increase , decrease or remain unchanged when anaesthesia is maintained with propofol . As the vasodilatory and myocardial depressant effects are concentration dependent the decrease in blood pressure from propofol during the infusion phase is much less then that seen following an induction bolus. An infusion of propofol results in a significant reduction in both myocardial blood flow and myocardial oxygen consumption therefore the global myocardial O2 supply / demand ratio is preserved.

OTHER EFFECTS :

Propofol does not potentiate neuromuscular blockade produced by both nondepolarizing and depolarizing neuromuscular blocking agents. Propofol produced no effect on the evoked electromyogram or twitch tension; however , good intubating condition after propofol alone have been reported . Propofol does not trigger malignant hyperpyrexia and is the anaesthetic of choice in patients with this condition.

Propofol following a single dose or a prolonged infusion does not effect corticosteroid synthesis or alter the normal response to ACTH stimulation. Propofol in the emulsion formulation does not alter hepatic , hematologic or fibrinolytic function. Decrease in systemic blood pressure is the most significant side effect on induction with propofol .

Slow administration and lower doses in adequately prehydrated patients may attenuate the decrease in arterial pressure.

Propofol also possess significant antiemetic activity at low doses . Propofol at subhyphotic doses has also relieved cholestatic pruritius and was effective as noloxone in treating pruritus induced by spinal opiates.

Propofol cause a dose dependent decrease in the thermoregulatory threshold for vasoconstriction, but it has little effect on the sweating threshold.

Propofol only decreases polymorphonuclear leukocyte chemotaxis but not adherence phagocytosis and killing .

USES AND DOSES OF PROPOFOL

- Induction of GA — 1.5-2.5 mg/kg Intravenous
- Maintenance of GA — 80-150μg/kg/min Intravenous infusion
- Sedation — 10–50μg/kg/min Intravenous.
- Antiemetic — 10 mg intravenous

SIDE EFFECTS :

Pain on injection can be found with administration of propofol , it is reduced by using a large vein, avoiding veins in the dorsum of hand , adding lidocaine to the propofol solution and giving along with 5% dextrose infusion .

Myoclonus can occur after induction with propofol Apnoea following induction with propofol is common.

KETAMINE :

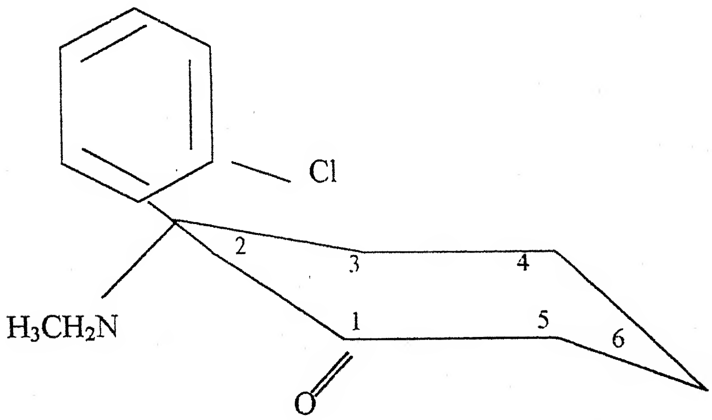
Ketamine was synthesized in 1962 by Stevens and first used in humans in 1965 by Corssen and Domino. It was chosen from among 200 phencyclidine derivative & proved to be the most promising in laboratory animal testing . It was released for clinical use in 1970.

PHYSIOCHEMICAL CHARACTERISTICS :

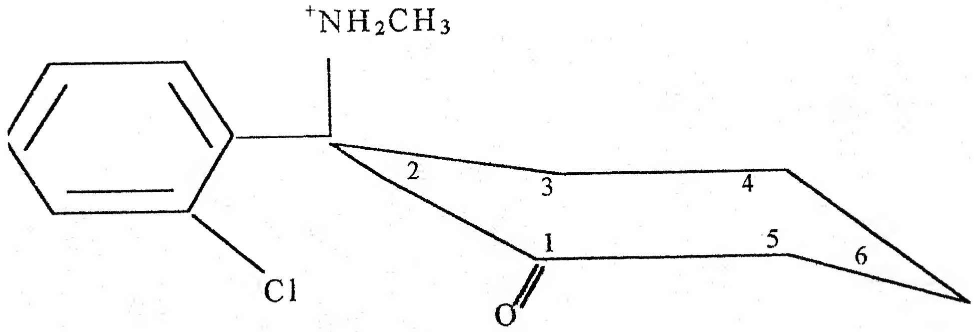
Ketamine has molecular weight of 238 , it is partially water soluble and forms a white crystalline salt with a pKa of 7.5 . It has a lipid solubility of 5-10 times that of thiopental , ketamine is prepared in a slightly acidic. pH 3.5 –5.5 solution and comes in concentrations of 10,50 and 100 mg/ml. The ketamine molecule contains a chiral center & occurs as 2 resolvable optical isomers or enantiomers. The commercial preparation being a racemic mixture of both isomers [S&R (-1)] in equal amounts .

The S (+) isomer elicit periods of hypnosis lasting nearly twice as long as the R(-) isomer following administration of equimolar doses , with the racemate being the intermediate potency .At equipotent dose, S(+) ketamine produced more profound analgesia and caused significant less post anaesthatic stimulation of counter activity in animals . S(+) ketamine has a higher concentration effect curve , White and associates suggested that the presence of R (-) ketamine in the racemate could exert an inhibitory

STERIO ISOMERS OF KETAMINE



S(+) Ketamine hydrochloride



R (-) Ketamine hydrochloride

influence on the recovery from the more potent S(+) enantiomer.

METABOLISM :

Ketamine is metabolised by the hepatic microsomal enzymes responsible for most of drugs detoxification.

The major pathway involves N- demethylation to form norketamine . These products are conjugated to water soluble glucuronide derivatives and excreted in the urine. norketamine has been show to have 20-30% activity of the parent compound .

PHARMACOKINETICS :

Regardless of the dose ketamine plasma disappearance can be described by a two compartment model. Ketamine has a rapid distribution reflected in the relatively brief slow distribution half life (t 1/2x of 11-16 minutes) . The high lipid solubility is reflected in its relatively large volume of distribution nearly 3 lit/kg . Clearance is also relatively high , ranging from 899 - 1,227 ml/min , which account for the relatively short elimination ½ life of 2-3 hrs.

The mean total body clearance (1.4 lit/min) is approximately equal to liver blood flow.

PHARMACODYNAMICS :

CENTRAL NERVOUS SYSTEM :

Ketamine produces dose related unconsciousness and analgesia the anaesthetised state has been termed dissociative anaesthesia because patients , who receive ketamine appear to be in cataleptic state. Patients have profound analgesia but keep their eyes open and maintain many reflexes.

Ketamine has a low molecular weight, a pka near the physiologic pH and relatively high lipid solubility , it crosses the blood brain barrier rapidly , and therefore has an onset of action within 30 seconds of administration . The maximal effect occurs in about 1 min . After ketamine administration pupils dilate moderately and nystagmus occurs. Lacrimation and salivation are common , as is increased skelatal muscle tone, often with coordinated but seemingly purposeless movements of the arms, legs , trunks and head.

Plasma levels of 0.6 – 20 mg/ml are considered the minimum concentration for general anaesthesia but children may require slightly higher plasma levels (0.8 – 4.0 μg/ml.).

The duration of anaesthesia after a single administration of a general anaesthetic doses (2mg/kg IV) is 10-15 mins and full orientation to person, place and time occurs within 15-30 mins.

Analgesia occurred at considerably lower blood levels than loss of consciousness . The plasma level at

which pain there should is elevated is 0.1 mg/ml. This means that there is a considerable period of post operative analgesia after ketamine general anaesthesia and that subanaesthetic doses can be used to produce analgesia .

The site of action appears to be the thalamoneocortical projection system.

It selectively depress neuronal function in parts of the cortex (especially association areas) and thalamus , while simultaneously stimulating parts of the limbic system including the hippocampus . This creates a functional disorganization.

There is also evidence that ketamine depresses transmission of impulses in the medial medullary reticular formation, important for transmission of the effective emotional components of nociception from the spinal cord to higher brain centers . There is some evidence that ketamine occupies opiate receptors in the brain centers . There is some evidence that ketamine occupies opiate receptors in the brain and spinal cord that could account for some of the analgesic effects.

Ketamime increases the cerebral oxygen consumption ($CMRO_2$) , cerebral blood flow and cerebrospinal fluid pressure . These changes are independent of any rise in blood pressure and persists even under halothane anaesthesia but can be blocked by thiopentone . Ketamine increases $CMRO_2$ due to its CNS effects which are detected on EEG (development of nerve activity) . The increase in intracranial pressure has been

attributed to the increase in cerebral blood flow as well as a generalised increased in sympathetic nervous system response. Cerebrovascular responsiveness to CO_2 appears to be preserved with ketamine , therefore reducing $paco_2$ which attenuate the rise in intracranial pressure after ketamine.

Failure to produce anaesthesia with ketamine occurs in patients where there is an absence of appropriate cerebral development , likewise it may be ineffective in neonates and very young children.

Ketamine like other phencyclidines, produces undesirable psychological reaction, there occur during awakening from ketamine anaesthesia and are termed emergence reactions. The psychological menifestations very in severity from a pleasant dream like state , floating feeling (extracorporeal experience) , vivid dreaming to hallucination and emergence delirium. These may be accompanied by delirium or irrational behaviour and may or may not be remembered . There are three related aspects of this problem. (1) Emergence reaction (2) Dreams and hallucinations and (3) long term psychomimetic effects.

1. Emergence delirium or excitement occurs in the immediate post operative period and the patients becomes disoriented restless and agitated. It is often accompanied by irrational talking or uncontrolled crying and moaning . The patients is usually unaware of their occurrence .

2. Vivid dreams or hallucination can occur up to 24 hours after ketamine . They have morbid content frequency and do upset the patient.
3. Long term psychomimetic effects are not well authenticated.

RESPIRATORY SYSTEM EFFECTS :-

Respiratory depression is minimal and transient after clinical doses of ketamine as reflected by an unaltered response to co_2 . However hypoventilation and a fall in paO_2 can occur after rapid injection of 2mg/kg.iv.

Unusually high doses may seldom produce apnoea. Arterial blood gases are generally preserved when ketamine is used alone for anaesthesia or analgesia. However with the use of adjuvant sedatives or anaesthetic drugs , respiratory depression can occur.

Ketamine dilates the bronchial tree and antagonizes the bronchoconstrictor effects of histamine, so that has theoretical advantages in anaesthesia for the asthamatic . Ketamine is as effective as halothane or enflurane in preventing experimentally induced bronchospasm. The mechanism for this effect is probably a result of the sympathomimetic response to ketamine . There is an increase in salivation following ketamine that can produce upper airway obstruction which is especially hazardous in children .It can be further complicated by laryngospasm. Although swallow , cough , sneeze and gag reflexes are relatively intact there is evidence that silent aspiration can occur during ketamine anaesthesia .

CARDIOVASCULAR SYSTEM EFFECTS :-

In contrast to almost all other intravenous induction agents , some degree of cardiovascular stimulation occurs almost invariably causing an increases in heart rate , stroke , volume , arterial blood pressure and myocardial oxygen consumption . The increases in cardiovascular function are associated with increased work and myocardial oxygen consumption . The normal heart is able to increase oxygen supply by increasing cardiac output and decreasing coronary vascular resistance so that coronary blood flow is appropriate for the increase in oxygen consumption.

The changes are not dose related as there is no difference in cardiovascular effects after administration of either 0.5 mg/kg intravenously . Second dose of ketamine produces haemodynamic effects less that or even opposite to the first dose. In patients with congenital heart diseases , there are no significant changes in shunt direction or systemic oxygenation after induction of anaesthesia with ketamine in vitro has negative inotropic effect, but the centrally mediated sympathetic responses to ketamine usually override the direct depressant effects of ketamine .The ketamine induced tachycardia and systemic hypertension can be blocked by adrenergic antagonists, vasodilators and benzodiazepines. It is also possible to lessen the tachycardia and hypertension produced by ketamine by using a continous infusion technique with or without a benzodiazepine. Ketamine can produce

haemodynamic depression in deep anaesthesia where sympathetic responses do not accompany its administration.

USES :-

INDUCTION AND MAINTANANCE OF ANAESTHSIA :-

Poor risk patients (ASA Grade IV) those with respiratory and cardiovascular system disorders (excluding ischemic heart disease) represent the majority of candidates for ketamine induction , particularly patients with bronchospastic airway disease or with haemodynamic compromises based either on hypovolemia or intrinsic myocardial disease (except coronary artery disease) . However the direct myocardial depressent effects of the drug can lead to paradoxical circulatory response in critically ill patients which makes it unsuitable for what was once considered a main indication.

Other cardiac disease that can be optimally managed with ketamine anaesthesia are cardiac tamponade and constrictive pericarditis . The fact that it preserves heart rate and right atrial pressure through its sympathetic stimulating effects makes ketamine an excellent anesthetic induction and maintenance drug in these settings .

SEDATION:-

Ketamine is the particularly suited for sedation of the paediatric patients in the preoperative room . Paediatric patients have less adverse emergence reaction than adults , making its use in paediatrics more versatile .

Hollister Cr et al , in 1974 reported the side effects of ketamine in paediatric anaesthesia. They demonstrated that the incidence of vomiting and emergence delirium was greater in older children and the side effects were minimal in children under age 11. The degree of postoperative analgesia was good.

SIDE EFFECTS AND CONTRANDICATION :

The psychological , emergence reaction are common side effects. Patients with increase intracranial pressure and with intracranial mass lesions should not receive ketamine because it can increase the intracranial pressure and has been reported to cause apnoea on this basis. Because ketamine has a propensity to cause hypertension and tachycardia with a commensurate increase in myocardial oxygen consumption it is contraindicated in patients with ischemic heart disease .

Likewise it is also contraindicated in patients with vascular aneurysms because of the possible sudden change in arterial pressure . Patients with psychiatric diseases such as schizophrenia or history of adverse reactions to ketamine or one of its congeners. also constitute a contraindication . Caution should be used in giving ketamine to a patient when there is possibility of post

operative delirium from other causes (e.g. delirium tremens ,head injury).

DOSES AND ADMINISTRATION :-

Ketamine can be administered intravenously intramuscularly , orally , rectally and nasally.

(1)Sedation and analgesia :

- 0.2-0.8 mg/kg IV over 2-3 min.
- 2-4 mg/kg m p.r.n.
- 10-20 mg/kg /min infusion.

(2)Induction of General Anaesthesia :

For induction of General Anaesthesia , ketamine is recommended in the following doses.

- 0.5-2mg./kg IV
- 4-6 mg./kg IM

(3)Maintenance of General Anaesthesia :

- 0.5 – 2 mg/kg IV p.r.n. with N2O 50% in O2
- 10-50 mg./kg /min IV infusion with N2O (50-70) % in O2
- 30-90 mg/kg /min IV infusion withoutN_2O.

Consciousness is lost in 2-4 minutes but the onset may be delayed for 6-8 minutes. Consciousness usually returns in about 10-15 minutes after normal therapeutic dose of 2 mg/kg but like the onset of anaesthesia , it is difficult to determine the exact moment when this occurs. Muscle tone

returns to normal first after which there may be a period when the patient seems distant and unaware of his surrounding . The final apparent return of full contact with the environment may be sudden and the time varies from a few minutes to over one hour after first evidence of awakening . Diplopia and other visual disturbances are frequently present on return of consciousness and can be both persistent and distressing .

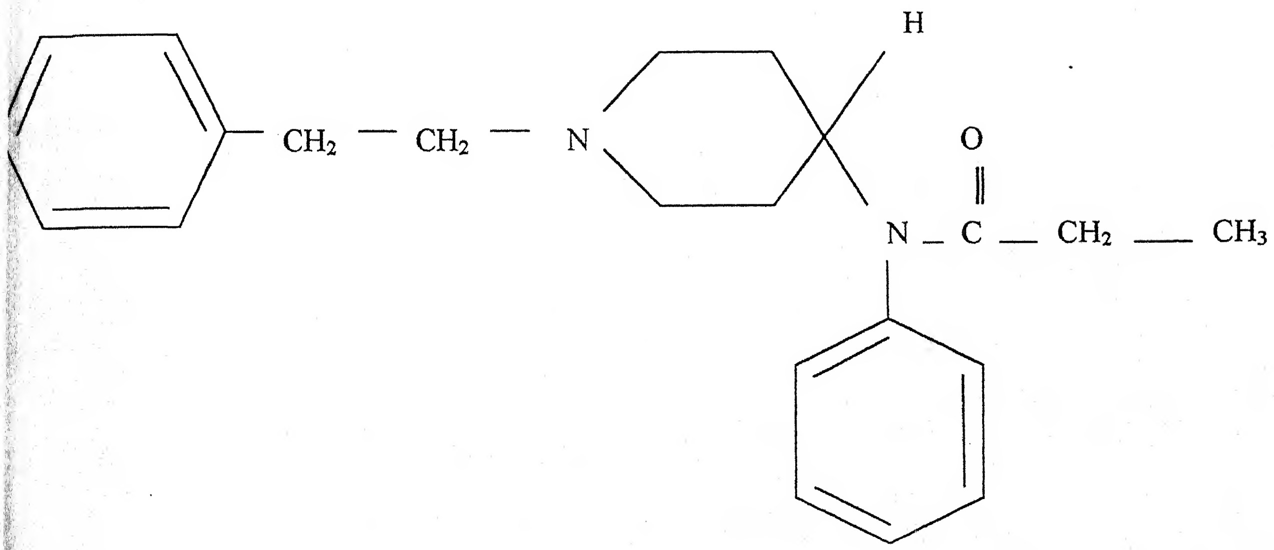
FENTANYL :-

Fentanyl citrate is a synthetic phenyl piperidene opioid analgesic and a chemical congener of the reversed ester of pethidine (meperidine) . It is primarily a mu(μ) opiate receptor agonist with an analgesic potency greater than morphine pethidine or alfentanil . Analgesia is produced principally through interaction with mu receptor at supra spinal sites. Fentanyl also binds to much lesser degree to the kappa (K) opioid receptor located with in the spinal cord . The kappa receptor mediates sedation and miosis but does not affect respiratory rate, heart rate, body temperature or gastrointestinal system . It is both potent and safe. The short duration of action of fentanyl is also highly advantageous in the setting of anaesthesia .

Comparative pharmacological characteristic of selected opioids.:-

Agent	Analgesic dose MED_{50} (mg/kg)	Anaesthetic dose MED_{50} dose (mg/kg)	Safety margin
Fentanyl	0.011	0.0012	160
Alfentanil	0.044	0.005	50
Pethidine	6.04	0.45	0
Morphine	3.21	1	33

Distribution :- Fentanyl and its derivatives readily cross the blood brain barriers. It is rapidly distributors to body



Fentanyl citrate

tissues. The relatively poor blood flow to fatty tissues limits the rate of medications accumulation in these tissues.

Protein binding –80-89% primarily bound to albumin and lipo proteins; dependent on plasma pH of drugs.

ONSET OF ACTION :-

1.For analgesic effects –

- Intramuscular – 7-15 min.
- Intravenous – 1-2 min.
- Epidural / spinal – 4-10 min.

2. Induction doses - Dependent on rate of administration 4-5 minutes when administered intravenously at a rate of 400 mcg per min.

TIME TO PEAK EFFECT :-

1.Analgesic-effect - Intramuscular 20-30 min.
Intravenous 3-5 min
Epidural /spinal <30 min.

2.Respiratory depressent effect-
5-15 minutes following administration of single intravenous dose.

DURATION OF ACTION :-

1. Analgesic effects (anaesthetic adjunct doses)
   - Intramuscular 1-2 hour
   - Intravenous 0.5-1 hour
   - Epidural / spinal - 1-2 hours(single dose of up to 100mg)

The amount of fentanyl which is equinalgesic with 10 mg morphine , is of the order of 0.2 mg (Morrison loan and dundee , 1971) while Lee and Alkin son (1977) mention that 0.05 mg fentanyl has the analgesic potency of morphine 10 mg or pethidine 100 mg.

DOSES :-

Premedication:-

- Intravenous/ Intramuscular 25-100 µg (0.7-2.0 µg/kg)

Analgesia :-

- Intravenous /Intramuscular 25-100µg /hr (0.7-2.0 µg/kg).
- Infusion 15-150 µg/hr (0.3-3.0µg/kg/hr)

Induction -

- Intravenous –5-40µg /kg
- Infusion - 0.25 –2.0 µg/kg/min for < 20 min . Titrate dose to patient response.

Anaesthesia supplement –

- Intravenous 2-20 µg / kg
- Infusion 0.025 –0.25 µg /kg /min.

SIDE EFFECTS :-

Like other opioids Fentanyl may produce nausea and vomiting at analgesic doses by stimulating chemoreceptor trigger zone.

Respiratory depression is marked , apnoea being common with doses in excess of 0.009 mg/kg , can be antagonized by nalorphine and its congeners. It depresses the respiratory centre in the brain stem and decrease respiratory rate, tidal volume, minute ventilation and ventilatory response to carbon dioxide . Fentanyl has little effects on heamodynamic stability (Pry's Roberts and Kelman 1967, Tommisto et al , 1970) and it reduces both cerebral blood flow and cerebral oxygen consumption (Michenfeldes and Theye 1971) Fentanyl causes alteration in arterial oxygen saturation as observed by "Pan PH, James CF " (1994) in their studies on pulse oximetry Adams AP , Pybus DA (1978) also observed delayed respiratory depression after use of fentanyl during anaesthesia which is menifested by decrease in arterial oxygen saturation .

Rigidity of the thoracic and abdominal muscles to an extent which makes inflation of lung difficult, has been reported after rapid intravenous infection of fentanyl (Corssen et al, 1994) . This is presumably a manifestation of stimulation of spinal reflexes and if it occurs it can be abolished by the use of muscle relaxant.

Material and Methods

MATERIAL AND METHODS

The present study was conducted on 60 young adult patients admitted in various surgical wards in M.L.B. Medical College and hospital, Jhansi.

Selection of cases

The patients selected for study were those kept for surgery by various surgical departments viz general surgery, gynaecology and orthopaedics. These patients belonged to ASA grade I and II, of either sex, between the age groups of 20-60 years.

Careful clinical history and physical examination was done to exclude any cardiovascular and respiratory disease and their age, sex, weight, baseline haemodynamic and respiratory variables were recorded. The patients suffering from any psychiatric illness and hypertension were excluded from the study. These patients were subjected to various routine investigations for that age group viz haemogram, blood sugar, blood urea, serum creatinine, urine for routine and microscopic examination, ECG and chest X-ray. The procedure and possible risks were explained to the patients as a part of an informed written consent for anaesthesia and surgery. Patients were kept

fasting 8 hours prior to surgery. These patients were allocated randomly into two groups as follows :

Group-I :- Patients were induced with propofol and ketamine.

Group-II :- Patients were induced with propofol and fentanyl.

Trade name of drugs used :

1. Profol 1% (Claris lifesciences limited)
2. Trofentyl (Troikaa Parenterals Pvt. Limited)
3. Ketamine (Neon Laboratories Limited

Premedication : All patients were premedicated with:

- Injection glycopyrolate slow intravenous in the dose of 0.2mg, 5 minutes prior to surgery.
- Injection medazolam slow intravenous in the dose of 2.0mg, followed by injection glycopyrolate.

Method

Each patients was reviewed thoroughly before conduct of anaesthesia. Patients were placed in supine position and an intravenous line was established with 18 guage i.v. canula 5% dextrose. Necessary monitoring gazzetes were connected to the patients, viz pulse oximeter

(ohmada) and non invasive blood pressure instrument pulse rate, arterial blood pressure, respiratory rate and arterial oxygen saturation were recorded. Now patients of both group were premedicated as mentioned earlier.

Group-I

Patients of group-I were induced with ketamine 0.5mg/Kg body weight over a period of 15 seconds followed by propofol 3mg/Kg body weight bolus till the end point of induction was reached (i.e. loss of consciousness and loss of eyelash reflex). Infusion of propofol at a rate of 3mg/minute was started immediately with infusion pump. When patient responds to pain, sweating, lacrimation, limb movements, a bolus of one fifth the original dose of ketamine was given. Airway maintained with head and neck positioning and spontaneous breathing was maintained with air. If oxygen saturation fell below 97% then 100% oxygen was given by mask, while patient breathing spontaneously.

Group-II

Patients of group-II were induced with fentanyl 1μg/Kg body weight over a period of 15 seconds followed by propofol 3mg/Kg body weight bolus till the end point of induction was reached (i.e. loss of consciousness and

loss of eyelash reflex). Infusion of propofol at a rate of 3mg/minute was started immediately with infusion pump. When patients responds to pain, viz increased heart rate, increased respiratory rate, sweating, lacrimation, limb movements a bolus of one fifth of original dose of fentanyl was given. Airway maintained with head and neck positioning and spontaneous breathing was maintained with air. If oxygen saturation fell below 97% then 100% oxygen was given by mask while patient breathing spontaneously.

The following parameters were observed and recorded.

- Induction time.
- Induction dose and total dose of propofol.
- Top up doses of ketamine and fentanyl.
- Continuous monitoring of pulse rate, arterial blood pressure, respiratory rate and arterial oxygen saturation was done throughout peri-operative period and readings were recorded at following time interval.
    - Before induction
    - One minute after induction
    - Five minutes after induction
    - Ten minutes after induction

- Twenty minutes after induction
- Immediate post –operative period.

- Recovery time:- The time at which each patient was able to open the eyes, responds to verbal commands and able to tell his or her name after the with-drawl of propofol infusion.
- Post operatively patients were enquired about acceptance. Patients were asked if they had slept well and asked about their experience pleasant or unpleasant during the recovery period.
- Post operative pain relief in immediate post-operative period judged by requirement of analgesic in immediate post operative period.
- Side effects or complications.

Observations

OBSERVATIONS

TABLE - I

Distribution of patients according to Age and Sex

Age (Years)	No. of patients						Total	% age
	Group –I			Group –II				
	Male	Female	Total	Male	Female	Total		
20-29	18	6	24	3	6	9	33	55
30-39	2	1	3	10	8	18	21	35
40-49	-	-	-	2	1	3	3	5
50-59	2	1	3	-	-	-	3	5
Total	**22**	**8**	**30**	**15**	**15**	**30**	**60**	**100**

Table-I shows that minimum number of patients 33 (55%) belong to 20-29 years of age group. Out of 60 patients 37 (67.67%) were male and 23 (38.33%) were female.

DISTRIBUTION OF PATIENTS ACCORDING TO AGE AND SEX

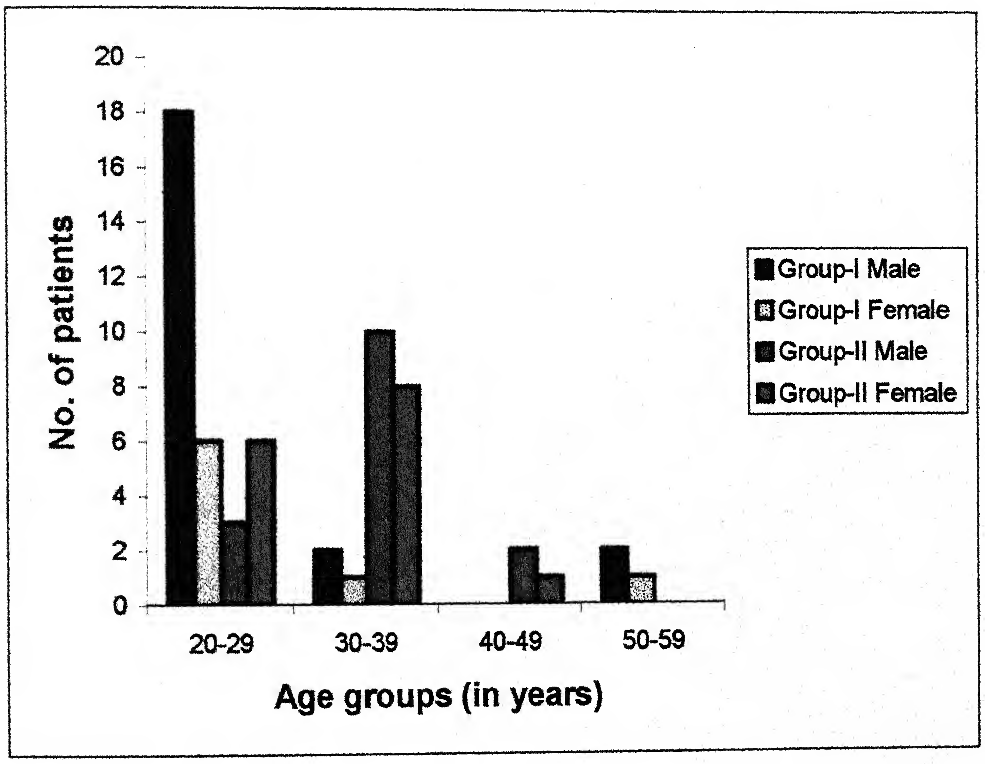


TABLE-II

Distribution of patients according to body weight

Weight (Kg)	Number of patients			
	Group-I	Group-II	Total	% age
41-50	10	12	22	36.66
51-60	15	14	29	48.33
61-70	5	4	9	15.00
>70	-	-	-	--
Total	**30**	**30**	**60**	**100**

Table-II shows that maximum number of patients 29(48.33%) wee weighing between 51-60Kg in both the groups.

DISTRIBUTION OF PATIENTS ACCORDING TO BODY WEIGHT

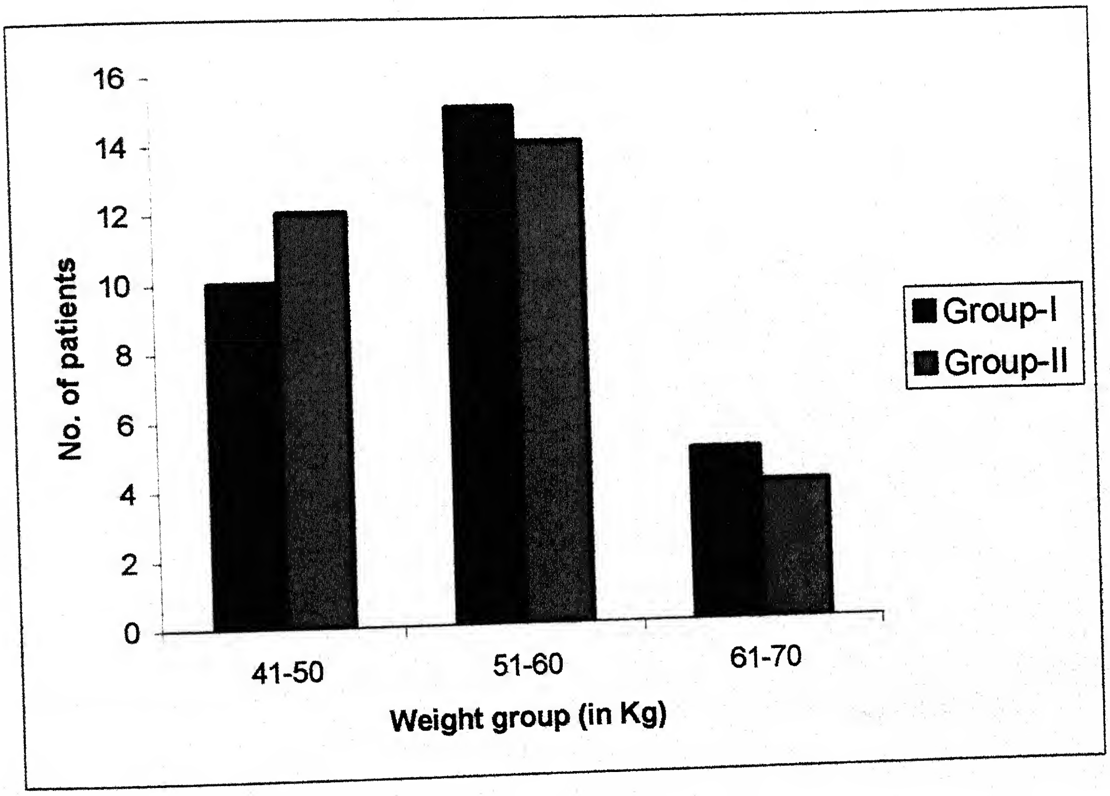


TABLE - III

Distribution of patients according to nature of surgery

Nature of surgery	Number of patients	
	Group-I	Group-II
Orthopaedic surgery		
Open reduction and internal fixation	6	4
Amputation	2	2
Sequestrectomy	4	3
Curratage	4	3
K-nail removal	2	2
General Surgery		
Skin grafting	5	5
Gynaecological surgery		
MTP and Ligation	7	11
Total	**30**	**30**

Table-III shows that maximum number of cases had undergone for orthopaedic surgery i.e. group-I 18 (60%) and group-II 14 (46.6%). All the surgical procedures were of about same duration.

DISTRIBUTION OF PATIENTS ACCORDING TO NATURE OF SURGERY

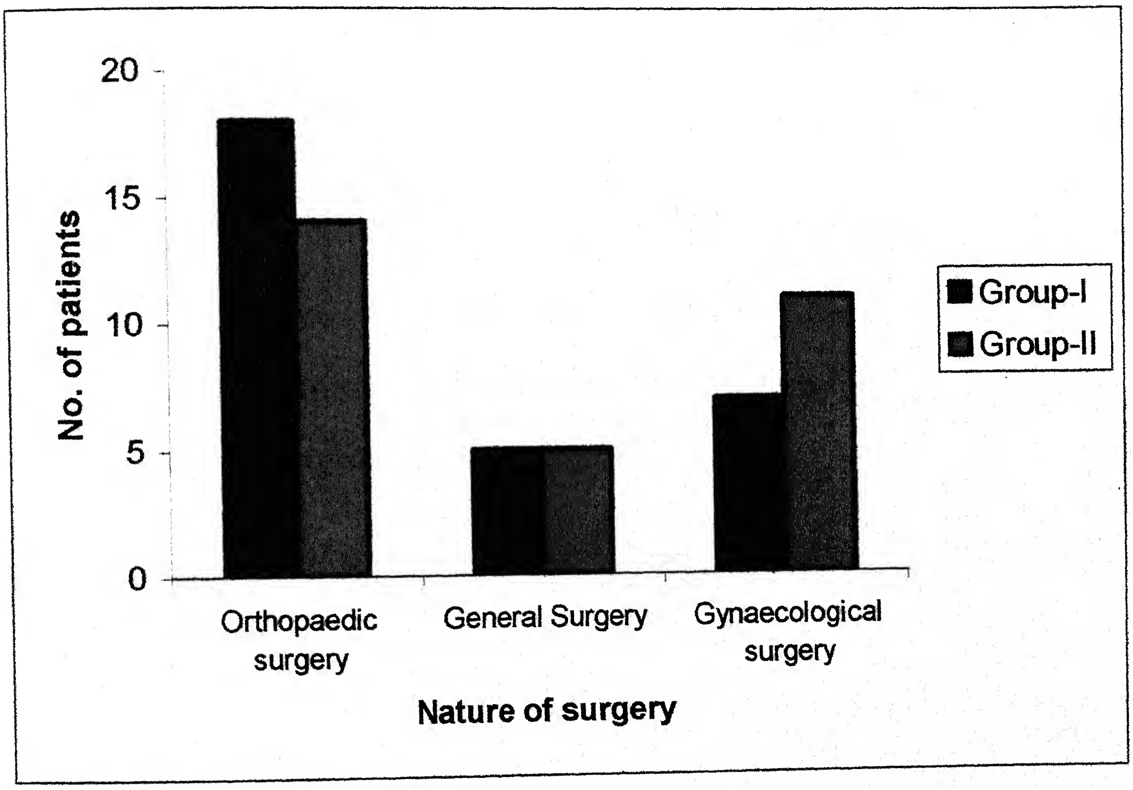


TABLE - IV

Time for onset of induction (mean±SD second)

	Group-I	Group-II
Time (Seconds) Mean ±SD	43.8±5.90	50.5±6.76***

*** Denotes highly significant ($p<0.001$).

Table-IV shows that time for onset of induction in group-I (propofol-ketamine) 43.8±5.90 as compared to in group-II (propofal-fentanye0 50.5±6.76.

Difference between group-I and group-II was statistically highly significant ($p<0.001$).

TIME FOR ONSET OF INDUCTION IN DIFFERENT GROUPS

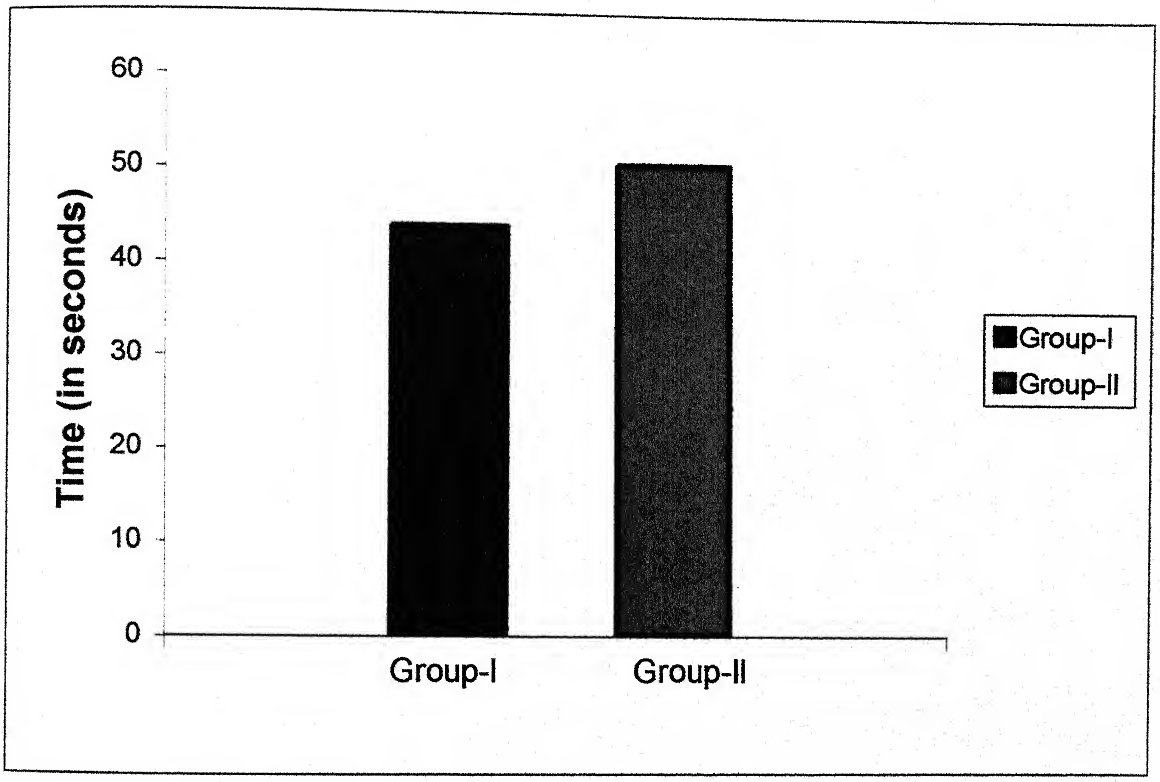


TABLE - V

Total and induction dose of propofol and number of top up doses of ketamine and fentanyl (mean±SD)

	Group-I	Group-II
Induction dose of propofol (mg)	142.0±12.70	155.0±18.89**
Total dose of propofol (mg)	223.0±10.20	236.0±12.22**
Number of top ups of ketamine and fentanyl	2.20±1.4	3.50±1.8

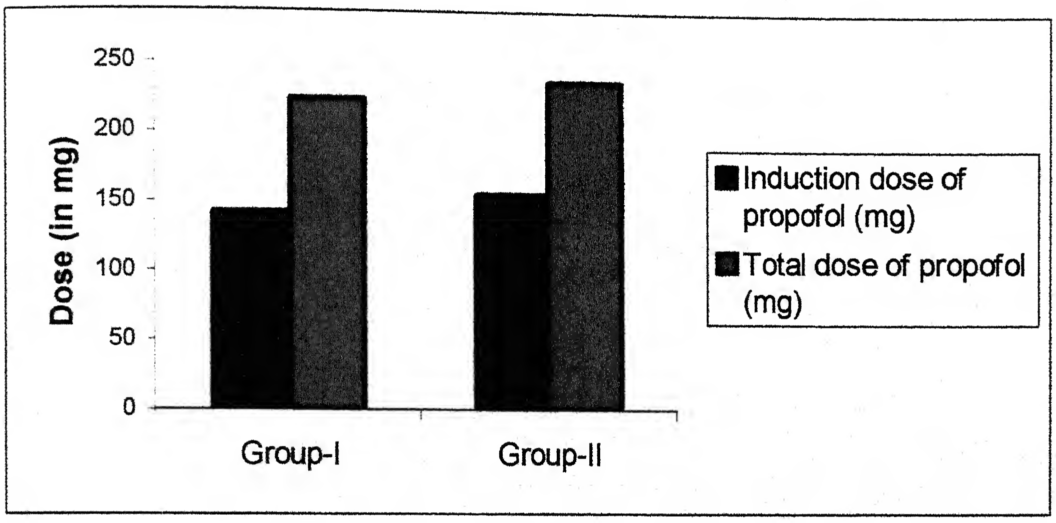
** Denotes significant value ($p<0.05$)

Table-V shows that induction dose of propofol in group-I was 142.0±12.70 and group-II was 155.0±18.89. Total dose of propofol in group-I was 223±10.20 and group II was 236.0±12.22. And number of top up doses of ketamine in group-I was 2.20±1.4 and fentanyl in group II was 3.50±1.8.

The mean induction dose of propofol and total dose of propofol were less in group I as compared to group – II. The difference between both the group was statistically significant ($p<0.05$).

The difference between number of top-up doses of ketamine and fentanyl in group–I and group-II, respectively was not significant.

TOTAL AND INDUCTION DOSE OF PROPOFOL IN DIFFERENT GROUPS



NUMBER OF TOPS UPS OF KETAMINE IN GROUP-I AND FENTANYL IN GROUP-II

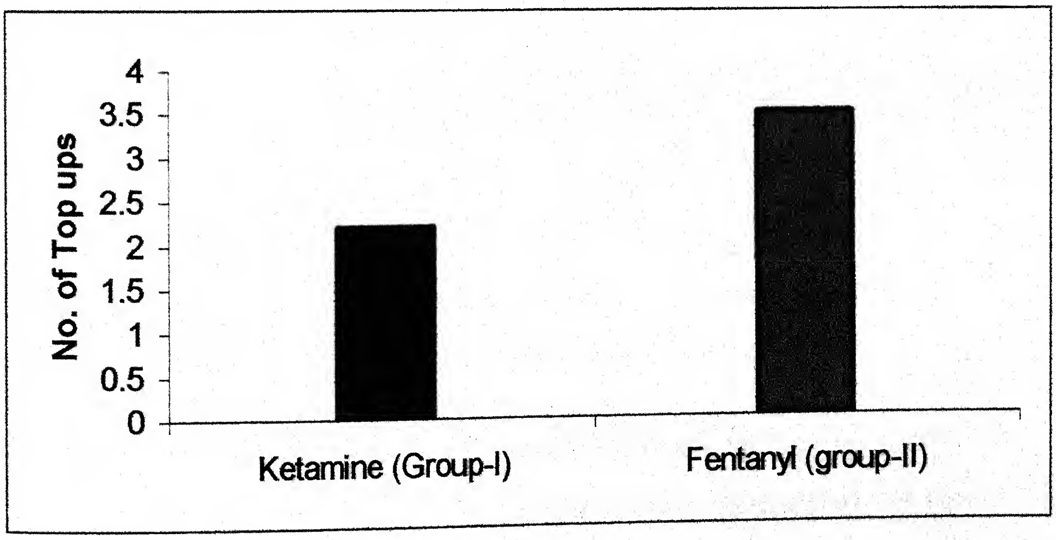


TABLE-VI

Changes in mean pulse rate (Mean±SD /min)

Time interval	Group-I	Group-II
Pre induction	92.20±9.85	92.00±8.33
1 min after induction	90.20±8.05	79.4±7.50***
5 min after induction	88.0±8.38	87.4±7.50***
10 min after induction	87.2±8.29**	86.8±7.51***
20 min after induction	87.8±7.41	89.00±7.46
Immediate post operative	87.6±7.54	88.80±8.87

** Denotes significant change ($p<0.05$)

*** Denotes highly significant change ($p<0.001$)

Table-VI shows that in group-I there was significant ($p<0.05$) fall in mean pulse rate at 10 minute after induction from pre induction level. There was no significant change at 1 minute, 5 minute, 20 minutes after induction and immediate post operative period.

In group-II there was highly significant ($p<0.001$) fall in mean pulse rate at 1,5 and 10 minutes after induction from pre-induction level and fall was insignificant ($p>0.05$) at 20 minutes after induction with propofol and in immediate post operative period.

CHANGES IN MEAN PULSE RATE

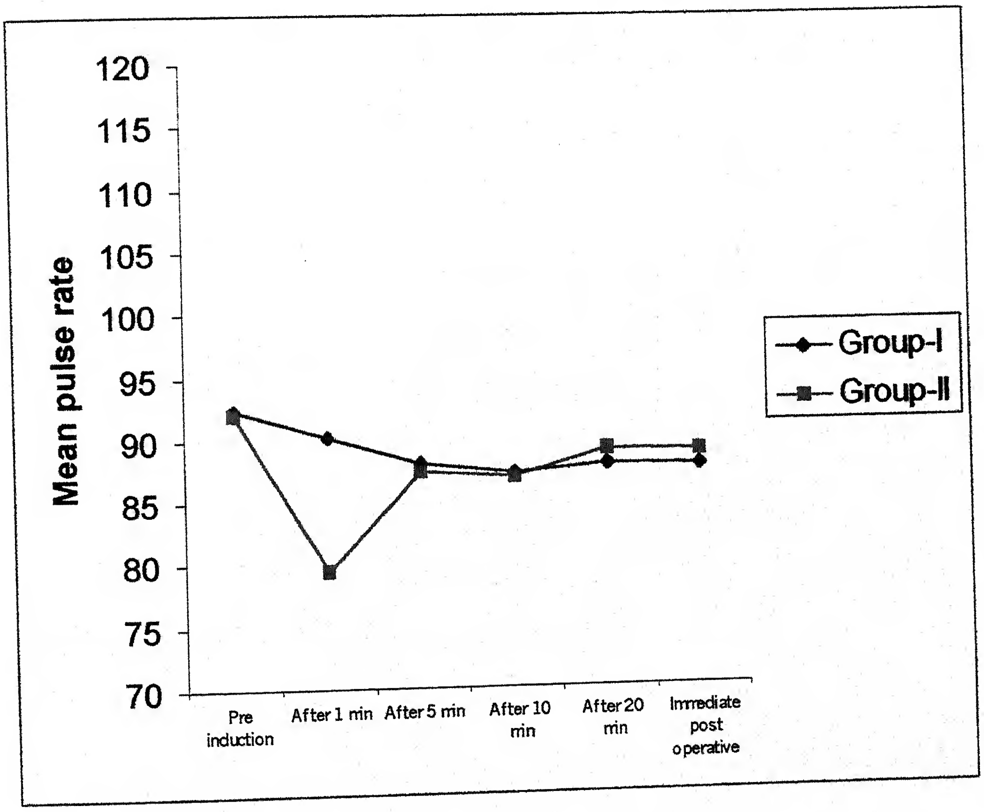


TABLE-VII

Changes in systolic and diastolic blood pressure (mean ±SD mmHg)

Time interval	Group-I	Group-II
Pre induction	127.80±7.95 / 85.00±6.76	129.0±9.97 / 85.4±4.98
1-min after induction	127.40±7.44 / 84.60±6.68	108.4±8.63*** / 68.0±5.78***
5 min after induction	127.80±7.95 / 85.00±6.76	111.0±9.54*** / 70.0±5.78***
10 min after induction	129.80±7.58 / 85.20±9.93	121.0±9.59** / 78.0±6.1**
20 min after induction	127.80±8.0 / 84.20±5.85	126.0±9.32 / 84.0±6.74
Immediate post operative	127.6±7.65 / 84.0±5.82	127.0±8.30 / 84.0±6.74

** Denotes significant change (p<0.05)

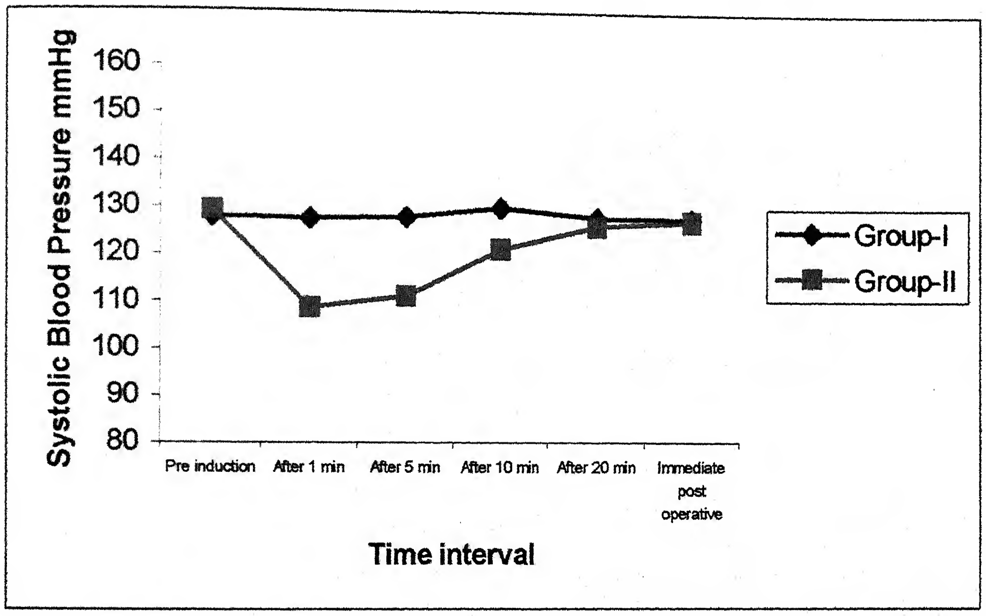
*** Denotes highly significant change (p<0.001)

Table-VII showing changes in systolic and diastolic blood pressure. In group-I the values of systolic and diastolic blood pressure did not show any significant change at 1 minute, 10 minutes, 20 minutes after

induction and in immediate post operative period as compared to pre-induction level.

In group II there was highly significant ($p<0.001$) fall in systolic and diastolic blood pressure at 1 and 5 minutes while fall is significant ($p<0.05$) at 10 minutes from pre induction level. And fall was insignificant ($p>0.05$) at 20 minutes after induction with propofol and in immediate post operative period.

CHANGES IN SYSTOLIC BLOOD PRESSURE



CHANGES IN DIASTOLIC BLOOD PRESSURE

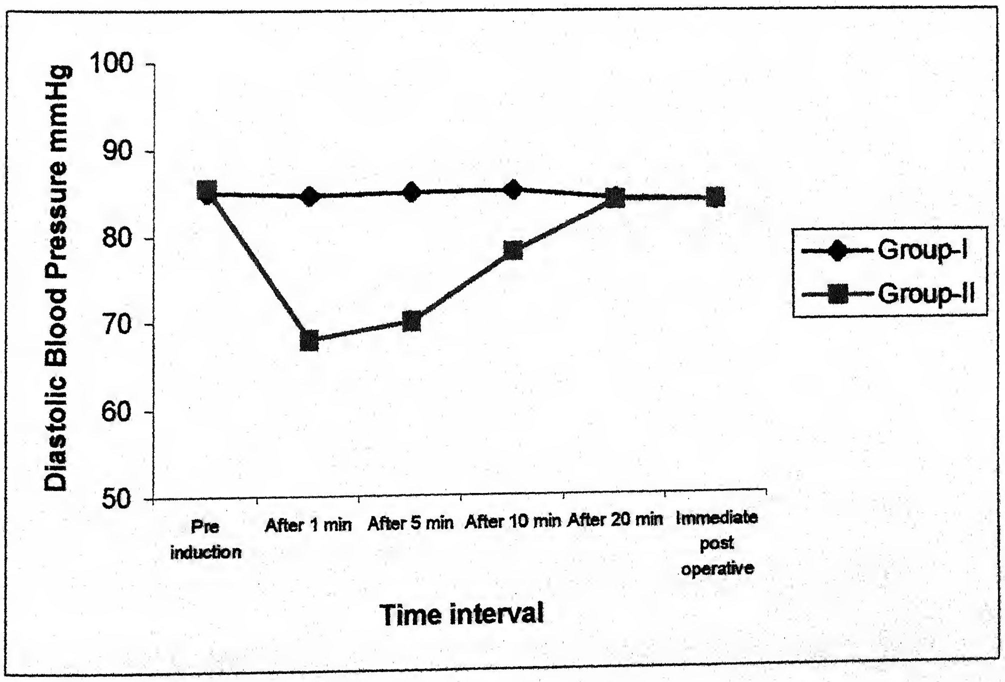


TABLE - VIII

Changes in mean arterial pressure (mean±SD mmHg)

Time interval	Group-I	Group-II
Pre induction	99.22±6.45	99.89±6.08
1 min after induction	98.83±6.33	81.61±5.73***
5 min after induction	99.22±6.45	83.6±3.90***
10 min after induction	100.29±5.31	92.29±6.77**
20 min after induction	98.7±6.38	97.93±7.24
Immediate post operative	98.51±5.80	98.3±6.24

** Denotes significant change (p<0.05)

*** Denotes highly significant change (p<0.001)

Table-VIII shows that in group I the value of mean arterial pressure did not show any significant change as compared to pre induction value. The values were statistically insignificant (p>0.05) at 1 minute, 5 minutes, 20 minutes after induction and in immediate post operative period as compared to pre induction value.

In group II there was highly significant (p<0.001) fall in mean arterial pressure at 1 and 5 minute while fall is significant (p<0.05) at 10 minute after induction from pre induction level.

CHANGES IN MEAN ARTERIAL PRESSURE

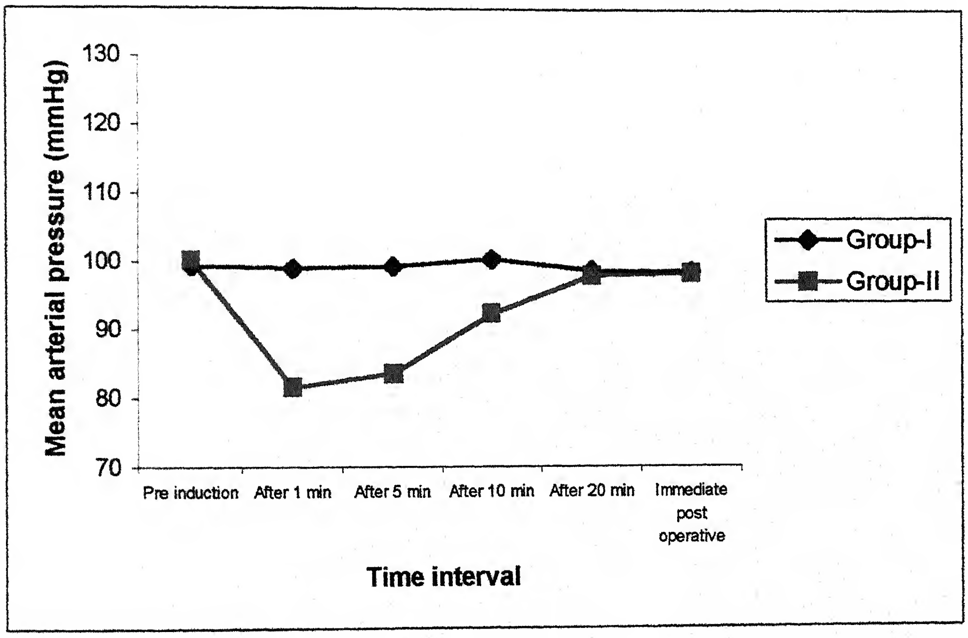


TABLE-IX

Changes in respiratory rate (mean±SD/ min)

Time interval	Group-I	Group-II
Pre induction	14.6±4.17	15.4±1.83
1 min after induction	15.0±3.11	12.2±1.68**
5 min after induction	15.4±2.41	13.2±1.34
10 min after induction	14.6±1.83	14.2±2.48
20 min after induction	14.8±1.62	14.6±4.17
Immediate post operative	14.20±2.48	14.6±1.83

** Denotes significant change ($p<0.05$)

Table-IX shows that in group-I there was no significant change in respiratory rate after 1 minute, 5 minutes , 20 minutes after induction as compared to pre induction value. In group-II there was significant ($p<0.05$) fall in respiratory rate at 1 minute after induction while the fall was insignificant at 5 minutes, 10 minutes, 20 minutes after induction as compared to pre induction value.

CHANGES IN RESPIRATORY RATE

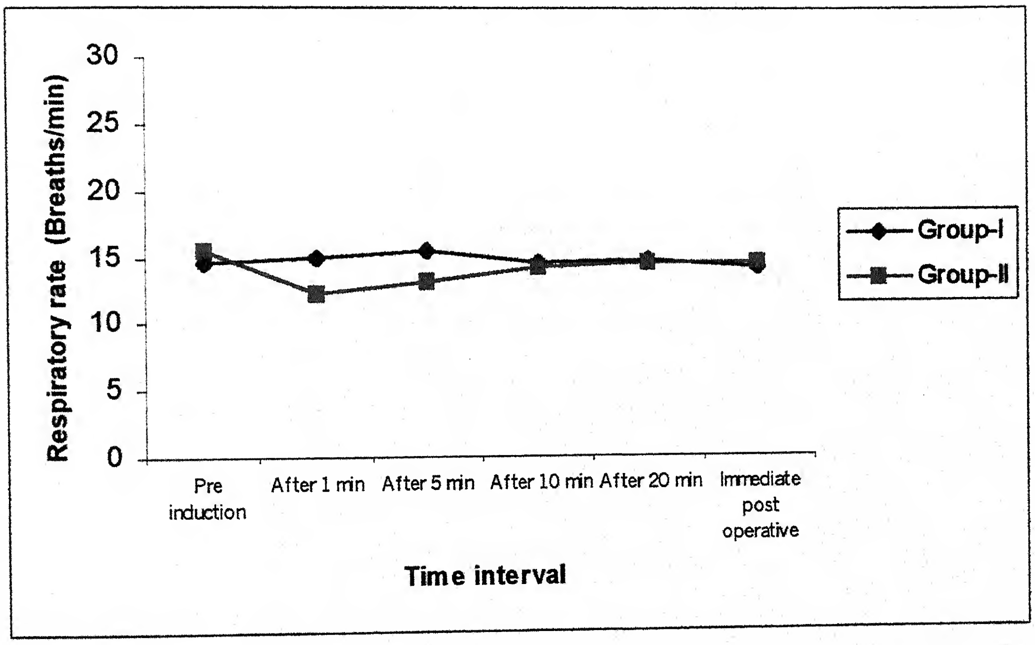


TABLE – X

Changes in arterial oxygen saturation (mean±SD % age)

Time interval	Group-I	Group-II
Pre induction	98.7±1.2	97.8±0.99
1 min after induction	98.7±1.2	97.4±1.3
5 min after induction	98.1±0.54	97.4±1.58
10 min after induction	98.1±0.54	97.4±1.53
20 min after induction	98.5±0.68	98.2±1.09
Immediate post operative	98.5±0.68	98.8±0.99

Table-X is showing values of arterial oxygen saturation at different times during intra-operative period. The oxygen saturation values are not showing any significant changes in both groups.

CHANGES IN ARTERIAL OXYGEN SATURATION

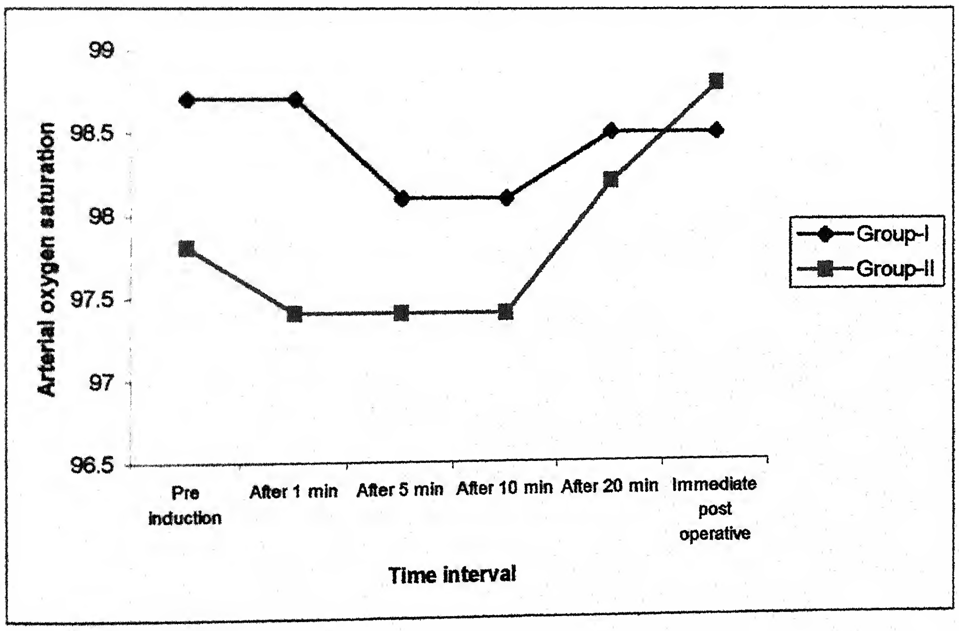


TABLE-XI

Time of recovery (mean±SD min)

Time (minutes)	Group-I	Group-II
Mean±SD	5.0±1.57**	3.6±1.99

** Denotes significant change

Table-XI shows that recovery time in group-I (propofol ketamine) was 5.0±1.57 as compared to group-II (propofol fentanyl) 3.6±1.99. Difference between group-I and group-II was statistically ($p<0.001$) highly significant.

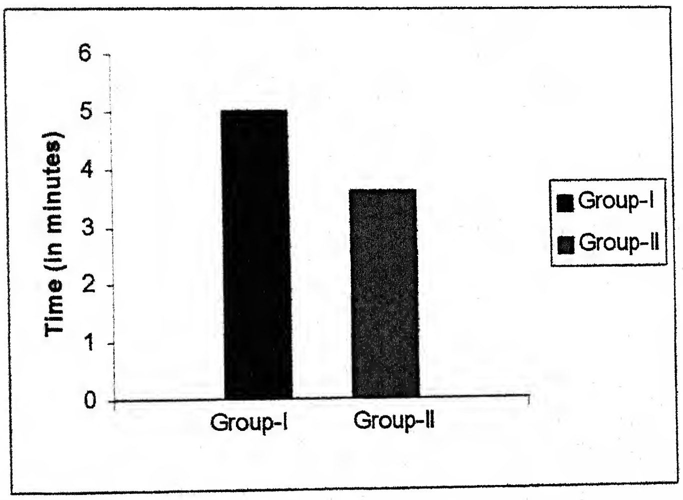
TABLE-XII

Analgesic requirement for post operative pain relief in immediate post operative period

	Group-I		Group-II	
	No.	% age	No.	% age
Analgesic requirement	1	1.66	4	6.66

Table-XII shows that analgesia was required by 1 patient (1.66%) in group-I and by 4 patients (6.66%) in group-II.

RECOVERY TIME IN DIFFERENT GROUPS



ANALGESIC REQUIREMENTS FOR POST OPERATIVE PAIN RELIEF IN IMMEDIATE POST OPERATIVE PERIOD

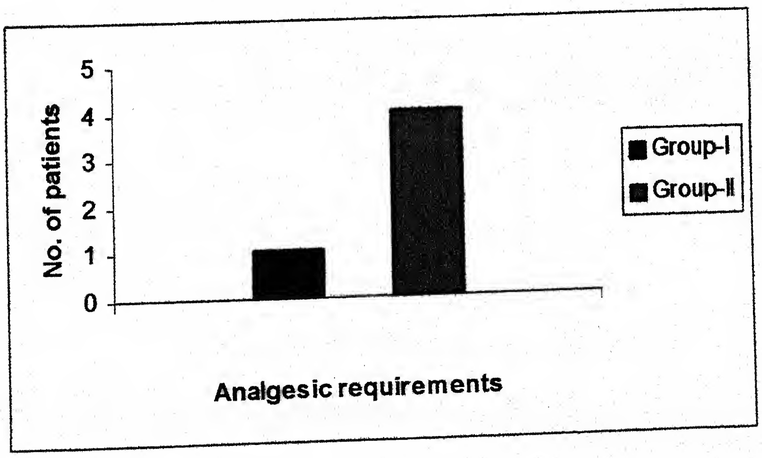


TABLE-XIII

Complications

Complication	Group-I		Group-II	
	No.	% age	No.	% age
Pain on injection	-	-	9	15
Laryngospasm	-	-	-	-
Episodes of desaturation	-	-	1	1.66
Apnea	-	-	1	1.66
Nausea & vomiting	-	-	4	6.66
Abnormal limb movement	1	1.66	-	-
Dreams	1	1.66	-	-

Table-XIII is showing complication and side effects observed in both groups during peri-operative and post-operative period.

COMPLICATION IN DIFFERENT GROUP

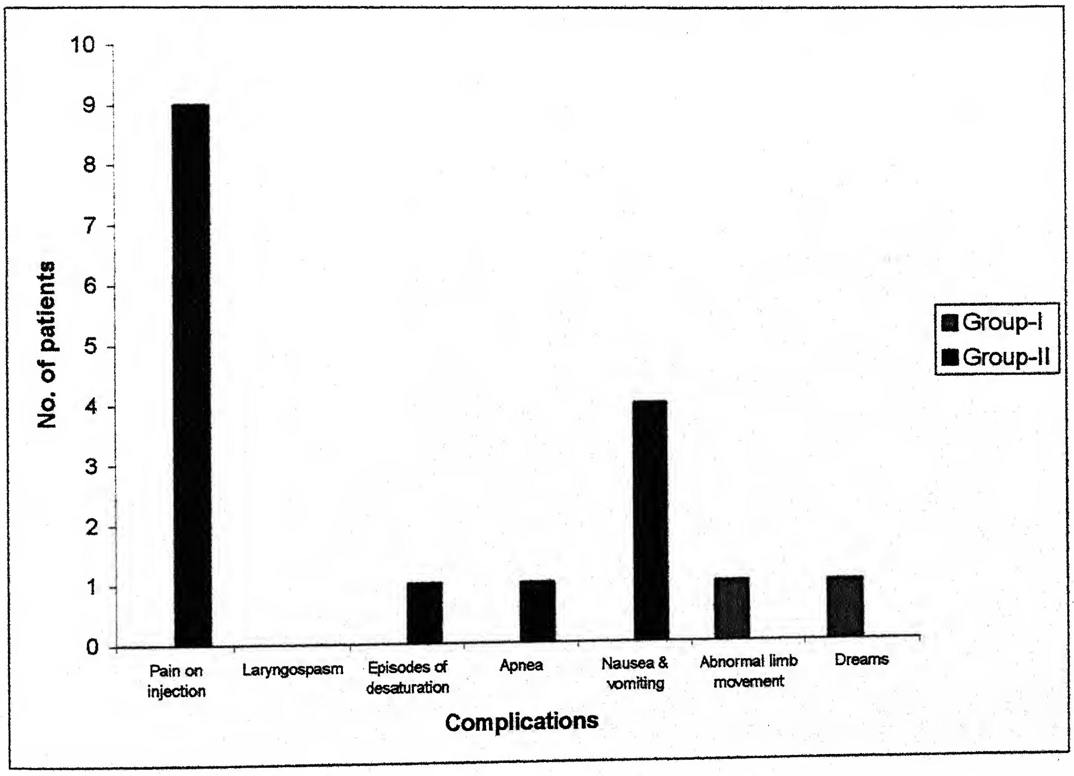


TABLE – XIV

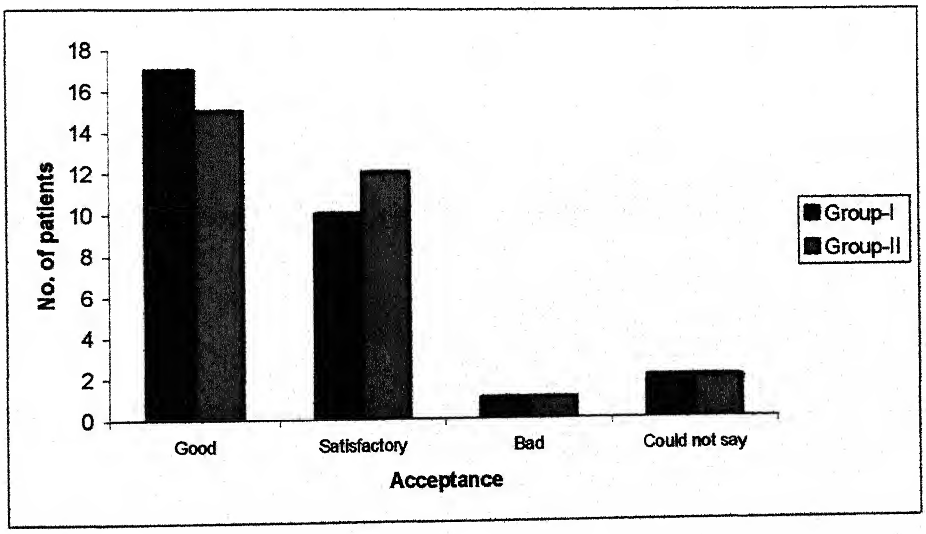
Patients Acceptance

Acceptance	Group-I		Group-II	
	No.	% age	No.	% age
Good	17	28.33	15	25.0
Satisfactory	10	16.66	12	20.0
Bad	1	1.66	1	1.66
Could not say	2	3.33	2	3.33

Table-XIV shows that anaesthesia was good in 17 patients (28.33%) in group I and 15 patients (25%) in group-II.

Anasethesia was found to be satisfactory in 10 patients (16.66%) in group-I and 12 patients (20.0%) in group-II and bad in 1 patient (1.66%) each in group-I and II. Two patients (3.33%) in group I and 2 patients (3.33%) in group II could not say.

PATIENTS ACCEPTANCE IN DIFFERENT GRPOUPS



Discussion

DISCUSSION

The concept of intravenous anaesthesia is attractive both for the patient as well as for the anaesthetist. For patient it had the advantage of producing loss of consciousness without excitement, distress or sensation of smoothering after produced by tightly pressed face mask. For the anaesthetist there is advantage of predictable anaesthesia which is rapid in onset without coughing or movement.

Total intravenous anaesthesia has gained popularity, partly in order to reduce pollution by volatile agents. Propofol has proven to be suitable as a hypnotic for TIVA. The drug has fast onset of action and rapid metabolism without accumulation. Also, the incidence of post-operative side effects i.e. nausea and vomiting are low. Propofol as no analgesic effect and is administered therefore in combination with a potent analgesic.

Ketamine in substancesthetic doses with propofol has gained attention in TIVA technique because of its powerful analgesic action in small doses without causing myocardial and respiratory depression. So it was though worth while to compare propofol in combination with ketamine from the popular combination i.e. propofol with fentanyl.

The analysis of data obtained from observation made on 60 patients of ASA grade I and II undergoing surgery under general anaesthesia, induced with either propofol and ketamine (group-I) or propofol and fentanyl (group-II) depicted that maximum number of patients (55%) belong to age group of 20-29 years and maximum number of patients (48.33%) were weighing between 51-60Kg. Out of 60 patients 37(61.67%) were male and 23(38.33%) were female though age and sex has no correlation with the selection of inducing agents.

In the present study, it was observed that induction of anaesthesia was faster with propofol and ketamine than the propofol and fentanyl. Mean induction time was 43.8±5.90 seconds in group-I while it was 50.5±6.76 in group II, this could have been because when propofol and ketamine were used in combination, are additive as hypnotic and anaesthetic end points and also because of onset of action is faster with ketamine than the fentanyl.

Propofol exert its action through GABA receptors. Propofol being highly lipophilic in nature rapidly crosses the blood brain barrier thus accounting for rapid onset of action. Ketamine is a potent analgesic, its anaesthetic and analgesic effects have been suggested to be mediated by

different mechanism. Ketamine interacts with N-methyl D-aspartate receptors, monoaminergic receptors, muscarnic receptors and voltage sensitive calcium channels. Analgesia produced by fentanyl is principally through interaction with mu(μ) receptor at supraspinal sites. Fentanyl also binds to much lesser degree, to the kappa (k) opioid receptor.

The doses used for induction was fixed accordingly to body weight to reach the induction criteria i.e. loss of consciousness and loss of eyelid reflex; propofol in the dose of 3mg/Kg body weight ketamine in the dose of o.5mg/Kg body weight and fentanyl in the dose of 1.0 μg/Kg body weight. The infusion rate of propofol for the maintenance of anaesthesia was 3mg/minute. The induction dose of propofol was less in group-I, 142.0±12.70 as compared to group-II, 155.0±18.89. Total dose of propofol was also less in group-I, 223.0±10.20 as compared to in group-II, 236.0±12.22. Number of top ups of ketamine in group-I was less than the number of top-ups of fentanyl in group-II. This could have been because when propofol and ketamine were used in combination, additive at hypnotic and anaesthetic end points.

The doses were almost similar and findings are in agreement with the work of Guit JBM et al (1990), Robert k Stoelting (1999), Sicignano A et al (1990), Hui TW et al (1995). Hamdani GA et al (1999) used ketamine in a dose of 0.3mg/Kg and was thought to be inadequate to provide sufficient analgesia for the surgical stimulus. They used propofol in dose of 2mg/Kg body weight and fentanyl 1.0μg/Kg body weight. Saha K et al (2001) use ketamine in the dose of 0.5mg/Kg body weight and fentanyl in the dose of 1.5μg/Kg body weight and found that dose of propofol for induction of anaesthesia with ketamine was less as compared with fentanyl.

Following administration of propofol and fentanyl i.e. group-II there was highly significant fall ($p<0.001$) in mean pulse rate at 1 minute, 5 minutes and 10 minutes after induction from pre-induction value as compared to in group-I where there is no significant fall in mean pulse rate after induction. This may be because ketamine causes some degree of sympathetic stimulation, which tends to counter balance, the cardiovascular effects of propofol. The findings are in agreement with the studies of Schuttler J et al (1991), Mayer M et al (1990) and Hernandez C et al (1999). Saha et al, found reduction in pulse rate after 5 and 10 minutes after induction with propofol & fentanyl.

Fall in systolic blood pressure was highly significant in group-II at 1,5 and 10 minutes after induction from premedication value as compared to in group-I where there was no significant change after induction.

In group-I there was no significant change in diastolic blood pressure as compared to in group-II as there was highly significant fall ($p<0.001$) at 1 and 5 minutes and fall was significant ($p<0.05$) at 10 minutes after induction from pre-induction value.

In group-I there was no significant change in mean arterial pressure after induction as compared to in group-II where there was highly significant fall ($p<0.001$) at 1 and 5 minutes and fall was significant ($p<0.05$) at 10 minutes after induction from pre-induction value. These findings are consistent with the work of Schuttler J et al (1991), Mayer M et al (1990) and Hernandez C et al (1999).

The intra-operative haemodynamic variables were found to be reasonably stable in group-I, this may be because of the counter balancing the cardiovascular effects of propofol by ketamine, which causes some degree of sympathetic stimulation. Patients in group-II showed a significant fall in haemodynamic variable which could be

because of the additive cardiodepressant effects of propofol and fentanyl.

In group-I there was no significant change in respiratory rate after induction while in group-II there was significant fall in respiratory rate at 1 minute after induction from pre-induction value. This fall may be because of respiratory depression produced by fentanyl. The findings are in agreement with Mayer Me et al (1990) and Hernandez C et al (1999) and Sternlo JB, et al (1998) found respiratory depression after total intravenous anaesthesia with propofol and alfentanil.

Arterial oxygen saturation readings in both the groups had not shown any significant changes after induction from pre-induction values.

In present study, the recovery time i.e. patients fully conscious and oriented to time, place and person in group-I (5.0±1.57) was longer than in group-II (3.6±1.99) and the difference was statistically significant. The prolonged recovery time in group-I could be because of longer elimination half life of ketamine as compared to fentanyl Janstrup M et al (1990), Hamdani GA et al (1999), Saha K et al (2001) have the same opinion about the recovery time

i.e. prolonged with propofol and ketamine combination than the propofol and fentanyl combination.

Post-operatively, analgesic for post-operative pain relief was required by 1 patient (1.66%) in group-I and by 4 patients (6.66%) in group-II. This may be because in fentanyl group analgesia was still inadequate as compared to ketamine group. The findings are in consistent with the work of Mayer M et al (1990).

In present study pain on injection was experienced by 9 patients (15%) in group-II during propofol injection as compared to none in group-I. In group-II pain on propofol injection may be due to alkaline nature of solution and more frequent when small veins are used for induction. In group-I no pain on propofol injection may be due to the local anaesthetic action of ketamine when administered intravenously as well as the central analgesic effect. This was in agreement with the findings of Tan CH et al (1998).

In present study episodes of desaturation occur in 1 patient (1.66%) in group-II as compared to none in group-I. Fentanyl causes alteration in arterial oxygen saturation as observed by Pan PH, James CF (1994).

Apnoea had occurred in 1 patient (1.66%) in group-I as compared to none in group-II. This may be due to

respiratory depressant action of fentanyl, this findings is consistent with the Adams AP, Pybus DA (1978).

Nausea and vomiting was found in 4 patients (6.66%) in group-I and none in group-II. As propofol posses significant antiemetic activity the presence of nausea and vomiting in group-II may be due to fentanyl at analgesic doses by stimulating chemoreceptor trigger zone. This is also comparable with the vomiting observed with the work of Badner NH, Bhandari R, Komer WE (1994). Propofol has been used successfully to treat post-operative nausea vomiting in abolus dose of 10mg by Borgert A et al (1992).

Dreams and emergence delirium was found in 1 patient (1.66%) in group-I as compared to none in group-II. Therefore in the present study propofol also seems to be effective in eliminating the adverse emergence reaction of ketamine in sub anaesthetic doses. This findings is consistent with the work of Guit JBM et al (1990) that propofol has proved to eliminate this adverse emergence reaction associated with ketamine.

Acceptance of induction phase was good in 15 patient (28.33%), satisfactory in 12 patients (20%) and 1 patient (1.66%) complained about bad experience and 2 patient

(3.33%) could not say in group-II. This comparison of acceptance is entirely subjective.

In group-I acceptance of anaesthesia was good in 17 patient (28.33%) satisfactory in 10 patient (16.66%) and bad in 1 patient (1.66%) and 2 patient (3.33%) could not tell.

Compared to patients of group I, patients of group-II remains sedated for prolonged period after surgery although they are arousable.

Thus it appears that combination of propofol and ketamine in total intravenous anaesthesia gives better haemodynamic stability during induction and maintenance of general anaesthesia, when compared with the use of propofol and fentanyl in combination, superior analgesia with less respiratory depression. However one of the main drawback with ketamine anaesthetic has been the emergence reaction, in the present study propofol also seems to be effective in eliminating the adverse emergence reaction of ketamine in subanaesthetic doses.

Conclusion

CONCLUSION

Following conclusions were inferred, when the study was completed and data was analyzed statistically:

i) Propofol and ketamine combination took less time (43.8±5.90 second) for time of onset of induction of anaesthesia in comparison with propofol and fentanyl combination (50.5±6.76 second).

ii) The induction dose and total dose of propofol was less in propofol ketamine i.e. 142.0±12.70mg and 223±10.20 mg respectively group as compared to in propofol fentanyl group where induction and total dose of propofol were 155.0±18.89 mg and 236±12.22.

iii) Number of top-ups of ketamine (2.20±1.4) were less than the number of top ups of fentanyl (3.50±1.8).

iv) Stability of pulse and blood pressure with propofol ketamine combination were comparable and better than with propofol fentanyl combination.

v) In propofol ketamine group respiratory rate was well maintained within normal range and no respiratory depression observed in comparison to propofol fentanyl group where significant respiratory depression was observed.

vi) Maintenance of arterial oxygen saturation was good with both the groups.

vii) Propofol ketamine combination took longer time i.e. 5.0±1.57 minutes for recovery from anaesthesia in comparison with propofol fentanyl combination (i.e. 3.6±1.99 minutes).

viii) Analgesic requirement for post-operative pain relief in immediate post-operative period was less (i.e. 1.6%) in propofol ketamine group in comparison to propofol fentanyl group (i.e. 6.66%).

ix) Incidence of complications like pain on injection, (15%) laryngospasm, (0%) episodes of desaturation, (1.66%) apnoea, (1.66%) nausea and vomiting (6.66%) are seen with propofol fentanyl combination. Abnromal limb movements (1.66%) and dreams (1.66%) are seen with propofol and ketamine combination.

x) The over all acceptance of anaesthesia was higher with propofol, ketamine (28.33%) than propofol, fentanyl (25%).

So to conclude, combination of propofol and ketamine gives better haemodynamic stability during induction and maintenance of total intravenous

anaesthesia. Subanaesthetic doses of ketamine may be an alternative, cheaper analgesic to supplement propofol anaesthesia, instead of short acting potent expensive opioids like fentanyl.

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Summary

SUMMARY

The present study was conducted on 60 young adult patients of ASA grade I and II, of either sex, in the age from 20 - 60 years admitted in various surgical wards of M.L.B. Medical College and Hospital, Jhansi. Patients were divided randomly into 2 groups :-

Group-I : Patients were induced with Propofol and Ketamine

Group-II : Patients were induced with Propofol and fentanyl

Patients were subjected to a thorough preanaesthetic check-up. Required investigation were done and an informed consent was taken. After maintenance of intravenous line, premedication was done with injection glycopyrolate (0.2mg) intravenously, 5 minutes prior to induction and injection midozolam (2.0mg) intravenously, followed by injection glycopyrolate. Patients of group-I were induced with ketamine (0.5mg/Kg body weight) intravenous over a period of 15 seconds followed by propofol (3mg/Kg body weight) intravenous bolus till the end point of induction was reached, infusion of propofol at a rate of 3mg/minute was started immediately with infusion pump. The same induction protocol was followed in group-II except fentanyl (1.0μg/Kg body weight) intravenous, was used for induction of anaesthesia instead

of ketamine. When patients responds to pain a bolus of one fifth of original dose of ketamine was given in group-I and fentanyl in group-II. Airway maintained with head and neck positioning and spontaneous breathing was maintained with air.

The following parameters were observed and recorded :

- Induction time.
- Induction dose and total dose of propofol.
- Top up doses of ketamine and fentanyl.
- Continuous monitoring of pulse rate, arterial blood pressure, respiratory rate and arterial oxygen saturation was done throughout peri-operative period and readings were recorded at following time interval.
- Before induction
- One minute after induction
- Five minutes after induction
- Ten minutes after induction
- Twenty minutes after induction
- Immediate post –operative period.
- Recovery time:- The time at which each patient was able to open the eyes, responds to verbal commands and able

to tell his or her name after the with-drawl of propofol infusion.

- Post operatively patients were enquired about acceptance. Patients were asked if they had slept well and asked about their experience pleasant or unpleasant during the recovery period.
- Post operative pain relief in immediate post-operative period judged by requirement of analgesic in immediate post operative period.
- Side effects or complications.

After analyzing the observed data, following conclusions were made:

i) Propofol and ketamine combination took less time (43.8±5.90 second) for time of onset of induction of anaesthesia in comparison with propofol and fentanyl combination (50.5±6.76 second).

ii) The induction dose and total dose of propofol was less in propofol ketamine i.e. 142.0±12.70mg and 223±10.20 mg respectively group as compared to in propofol fentanyl group where induction and total dose of propofol were 155.0±18.89 mg and 236±12.22.

iii) Number of top-ups of ketamine (2.20±1.4) were less than the number of top ups of fentanyl (3.50±1.8).

iv) Stability of pulse and blood pressure with propofol ketamine combination were comparable and better than with propofol fentanyl combination.

v) In propofol ketamine group respiratory rate was well maintained within normal range and no respiratory depression observed in comparison to propofol fentanyl group where significant respiratory depression was observed.

vi) Maintenance of arterial oxygen saturation was good with both the groups.

vii) Propofol ketamine combination took longer time i.e. 5.0±1.57 minutes for recovery from anaesthesia in comparison with propofol fentanyl combination (i.e. 3.6±1.99 minutes).

viii) Analgesic requirement for post-operative pain relief in immediate post-operative period was less (i.e. 1.6%) in propofol ketamine group in comparison to propofol fentanyl group (i.e. 6.66%).

ix) Incidence of complications like pain on injection, (15%) laryngospasm, (0%) episodes of desaturation,

(1.66%) apnoea, (1.66%) nausea and vomiting (6.66%) are seen with propofol fentanyl combination. Abnromal limb movements (1.66%) and dreams (1.66%) are seen with propofol and ketamine combination.

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So to conclude, combination of propofol and ketamine gives better haemodynamic stability during induction and maintenance of total intravenous anaesthesia. Subanaesthetic doses of ketamine may be an alternative, cheaper analgesic to supplement propofol anaesthesia, instead of short acting potent expensive opioids like fentanyl.